DRAFT

Consultative Document on Ethical Guidlines on Biomedical Rereasch involving Human Subjects

Indian Council of Medical Rereasch
New Delhi

1997

Not to be Quoted

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FOREWORD

Our generation shares the excitement of watching the profound transformation of our planet before our very eyes. Tools of scientific research are emerging as great instruments of enlightenment progressively demystifying the processes and products of evolution. All these generate a sense of great wonder and awe imparting, in a non-trivial sense, legitimacy to the teleological argument.

Genetic research is poised for a break-through in effective cancer treatment by combining Gene Therapy with Immunology. It is also predicated that in the next 50 years human life span would go up to 140 years.

But biological research on human subjects also hangs on a thin thread whose snapping might let loose an unstoppable hurtling to the unknown fraught with possibilities of some thing seriously going out of hand. Experiments on human subjects raise serious issues of

violation of basic human rights and issues of Confidentiality, Privacy, of the right to know and the duty to tell etc.

Genetic research is vigorously peeling off layer after layer of the unknown. It is in this context that ethical standards in Biomedical research involving human subjects assume significance, calling for rigorous standards and sanctions against mis-use and exploitation.

The Central Ethical Committee has endeavoured to update the earlier guidelines. Part 'A' contains a Statement of General Principles and Ethical Considerations in Medical Research involving human subjects. Part 'B' deals with Specific Ethical Principles in the areas of Human Genetics; Organ Transplantation including Foetal Tissue Transplantation; Clinical Evaluation of Drugs/ Devices/Vaccines/Herbal Remedies, etc; Epidemiological Research and Assisted Reproductive Technologies. The

Appendices in Part 'C' refer to documents of general interest on the subject.

The Committee presents the Draft Consultative Document on "Ethical Guidelines on Biomedical Research involving Human Subjects" for a purposeful and informed public debate to serve as a feed back before it can be given a final form. Indeed, in such an area with its fast expanding cantours, range and depth, the guidelines need to be updated constantly and as an ongoing exercise.

As Chairman of the Committee, I take this opportunity to thank the Members of the Committee and the Chairman and Members of the various Sub-Committees for their valuable contribution.

(M.N.Venkatachaliah)

New Delhi
24 December, 1997

PREFACE

The need for uniform ethical guidelines in research on human subjects has been well recognised, and at the present time this need is more acute because, apart from the mandatory clinical trials on new drugs, a number of diagnostic procedures, therapeutic interventions and preventive measures including the use of vaccines are being introduced which require proper testing on human beings.Further, the advent of new medical devices and radioactive materials as also the therapeutic benefits of recombinant DNA products have added a new dimension to ethical issues that need to be considered before evaluating these substances.

With the setting in of the era of biotechnology (including genetic engineering) medical procedures and therapeutics have undergone tremendous changes and many techniques based on these advances are no longer in the realms of science fiction, but have become a reality today. Recent advances in the field of assisted reproductive techniques, organ transplantation, human genome analysis and gene therapy offer unquestionable benefits to mankind but at the same time raise numerous questions of law and ethics, stimulating public interest and concern at various levels. On the one hand, there is a need to satisfy legitimate public concern, while on the other, one has to appreciate the need to encourage new scientific innovations for the benefit of mankind. It has therefore become imperative to provide specific guidelines for such research, taking into consideration all these new dimensions.

The **Indian Council of Medical Research** (ICMR) had brought out in February 1980, a document entitled, **Policy statement on ethical considerations involved in research on human subjects** prepared by the ethical committee under the chairmanship of Hon'ble Justice H.R.Khanna. This document has been widely used for 17 years by not only ICMR but also by other agencies and scientists. The document however needs to be updated in view of the recent developments in modern biology as also in different branches of medical science so that it could serve as an useful guide to all scientists and agencies involved in research on human subjects.

Therefore, a **Central ethical committee on human research (CECHR)** was constituted by the ICMR under the chairmanship of Hon'ble Justice M.N.Venkatachaliah to consider various issues related to the ethical, legal and social dimensions of research on human beings.The committee met on 10th September 1996 and identified following four major areas and the sub-committees for drawing up detailed guidelines:

1. Human Genetics research

2. Transplantation research including Fetal tissue transplantation

3. Clinical evaluation of Drugs/Devices/Vaccines/Herbal remedies

4. Epidemiological research

Apart from these the report of a separate committee drafting the technical and ethico-legal issues of **Assisted reproductive technologies** was also to be considered by this committee.

The CECHR met on 10th August 1997 to consider the draft reports prepared by all the five groups and following detailed discussions the present draft has been prepared for wide circulation and subsequent national debate before finalisation.

The Terms of Reference, list of Members of CECHR and the Sub-Committees are appended.

TERMS OF REFERENCE

a) To review ethical, legal, social and other issues of research involving/affecting human subjects.

b) To formulate general principles for such research.

c) To formulate guidelines on specific areas of such research.

d) To examine the possibilities of setting up machinery and mechanism to monitor, implement and review the general and specific guidelines so formulated, and to further formulate such guidelines as may be necessary from time to time.

e) To examine and review the guidelines, machinery and mechanisms so formulated in the light of experience gained from time to time.

f) To consider the wider implications of biomedical and health research and suggest ways and means in which inter-disciplinary and inter-agency dicussion and consultations can take place on an ongoing basis.

g) To consider ways and means in which these guidelines for research can be disseminated to increase awareness amongst researchers, concerned persons, institutions and the community.

LIST OF MEMBERS

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3. **Clinical evaluation of Drugs/Diagnostics/Vaccines/Herbal Remedies etc.**

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14.	Dr.B.N.Saxena, ICMR, New Delhi	Convener

Part A

General Principles

STATEMENT OF GENERAL PRINCIPLES IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

This **"Statement of Ethical Considerations involved in Biomedical Resarch on Human Subjects"** shall be known as the **ICMR Code** and shall consist of the -

(a) Statement of General Principles on Research using Human Subjects in Biomedical Research

(b) Statement of Specific Principles on Research using Human Subjects in specific areas of Biomedical Research

These Statements of General and Specific Principles may be varied, amended, substituted and added from time to time.

BACKGROUND

In the aftermath of the Second World War (1939-45), there was an intensified concern about the use of the human subjects for medical research. The first international statement on the ethics of medical research using human subjects was the **Nuremberg Code** of 1947, which emphasised consent and voluntariness. The Nuremberg Code was evolved in the aftermath of the trial of medical practitioners accused of conducting experiments in medical research without their consent and in conditions where the human subjects were put to grave risks resulting in their deaths and permanent impairment to their faculties. In 1948, **Universal Declaration of Human Rights** (adopted by the General Assembly of the United Nations) expressed human rights concern about human beings being subject to involuntary maltreatment. In 1966, the International Covenant on Civil and Political Rights specifically stated,*"No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected to without his consent to medical or scientific treatment"*.

Following preliminary efforts by the Council for International Organisations of Medical Sciences (CIOMS) the World Medical Association formulated the **Declaration at Helsinki** in 1964 which was revised from time to time and which laid down general principles on using human subjects in medical research in addition to specific prescripticns for biomedical research In February 1980, the **Indian Council of Medical Research** released a **"Policy Statement on Ethical Considerations involved in Research on Human Subjects"** for the benefit of all those involved in clinical research in India. In 1982, the World Health Organisation (WHO) and the CIOMS issued Proposed International Guidelines for Biomedical Research involving Human Subjects. Subsequently the CIOMS issued **"International Guidelines for Ethical Review of Epidemiological studies"** in 1991 and **"International Ethical Guidelines for Biomedical Research**

involving Human subjects" in 1993. Over the years, vario bodies in national jurisdictions have also laid down general a specific principles in respect of medical research generally a in specific areas of scientific research entailing the use human beings as a subject. These 'national' Codes (drawn fr the international codes and the universal principles underlyi them) outline 'guidelines' to be followed in their respecti jurisdictions.

GENERAL STATEMENT

Medical and related research using human beings as subject must necessarily ensure that -

(i) The **PURPOSE**, of such research is that it should be directe towards the increase of knowledge about the human conditio in relation to its social and natural environment, mindfu that the human species is one of the many species in planet in which the well being of all species is unde threat - no less from the human species as any other; an that such research is for the betterment of all, especiall the least advantaged.

(ii) Such research is **CONDUCTED** under conditions that no perso or persons become a mere means for the betterment of other and that human beings who are subject to any medica research or scientific experimentation are dealt with in manner conducive to and consistent with their dignity an well being under conditions of professional competence fair treatment and transparency; and, after ensuring tha the subject is placed at no greater risk, other than suc risk commensurate with the well being of the subject i question in the light of the object to the achieved.

(iii) Such research must be subjected to a regime of **EVALUATION** a all stages of the proposal *i.e.*, research design an experimentation, declaration of results and use of th results thereof; and, that each such evaluation shall bea in mind the objects to be achieved, the means by which the are sought to be achieved, the anticipated benefits an dangers, the potential uses and abuses of the experimen and its results and, above all, the premium that civilise society places on saving and ensuring the safety of eac human life as an end in itself.

STATEMENT OF GENERAL PRINCIPLES

Any research using the human beings as subjects of medica or scientific research or experimentation shall bear in mind th following principles -

I. **Principles of essentiality** whereby, the research entailin the use of human subjects is considered to be absolutel essential after a due consideration of all alternatives; i the light of the existing knowledge in the proposed area o

research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental well being of the planet.

II. **Principles of voluntariness, informed consent and community agreement** whereby, research subjects are fully apprised of the research and the impact and risk of such research on the research subject and others; and, whereby the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by such human subjects or someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding. Where any such research entails treating any community or group of persons as a research subject, these principles of voluntariness and informed consent shall apply, *mutatis mutandis*, to the community as a whole and to each individual member who is the subject of the research or experiment.

Where the human subject is incapable of giving consent and it is considered essential that research or experimentation be conducted on such a person incompetent to give consent, the principle of voluntariness and informed consent shall continue to apply and such consent and voluntariness shall be obtained and exercised on behalf of such research subjects by someone who is empowered and under a duty to act on their behalf.

The principles of informed consent and voluntariness are cardinal principles to be observed throughout the research and experiment, including its aftermath and applicative use so that research subjects are continually kept informed of any and all developments in so far as they affect them and others. However, without in any way undermining the cardinal importance of obtaining informed consent from any human subject involved in any research, the nature and form of the consent and the evidentiary requirements to prove that such consent was taken, shall depend upon the degree and seriousness of the invasiveness into the concerned human subject's person and privacy, health and life generally, and, the overall purpose and the importance of the research.

III. **Principle of non-exploitation** whereby, as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical risks as well as

moral implications of the research whether to themselves
others, including those yet to be born.

Such human subjects should be selected so that th
burdens and benefits of the research are distribute
without arbitrariness, discrimination or caprice.

Each research shall include an inbuilt mechanism fo
compensation for the human subjects either throug
insurance cover or any other appropriate means to cove
all foreseeable and unforseeable risks by providing fo
remedial action and comprehensive after-care, includi
treatment during and after the research or experiment,
respect of any effect that the conduct of research
experimentation may have on the human subject and to ensu
that immediate recompense and rehabilitative measures a
taken in respect of all affected, if and when necessary.

IV. **Principles of privacy and confidentiality** whereby, th
identity and records of the human subjects of the researc
or experiment are as far as possible kept confidential; and
that no details about identity of said human subjects
which would result in the disclosure of their identity, a
disclosed, without sound scientific reasons which may
essential for the purposes of therapeutics or othe
interventions,without the specific consent in writing of th
human subject concerned, or someone authorised on the
behalf; and, after ensuring that the said human subje
does not suffer from any form of hardship, discriminati
or stigmatisation as a consequence of having participat
in the research or experiment.

V. **Principles of precaution and risk minimisation** whereby, d
care and caution is taken at all stages of the research a
experiment (from its inception as a research idea, i
subsequent research design, the conduct of the research
experiment and its applicative use) to ensure that t
research subject and those affected by it are put to t
minimum risk, suffer from no irreversible adverse effec
and, generally, benefit from and by the research
experiment; and that requisite steps are taken to ensu
that both professional and ethical reviews of the resear
are undertaken at appropriate stages so that further a
specific guidelines are laid down, and necessary directio
given, in respect of the conduct of the research
experiment.

VI. **Principles of professional competence** whereby, the resear
is conducted at all times by competent and qualified perso
who act with total integrity and impartiality and who ha
been made aware of, and are mindful of, the ethic
considerations to be borne in mind in respect of su
research or experiment.

Principles of accountability and transparency whereby, the research or experiment will be conducted in a fair, honest, impartial and transparent manner after a full disclosure is made by those associated with the research or experiment of each aspect of their interest in the research, and any conflict of interest that may exist; and whereby, subject to the principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research inclusive of data and notes are retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring evaluation of the research, conduting further research (whether by the initial researcher or otherwise) and in order to make such records available for scrutiny by the appropriate legal and administrative authority, if necessary.

I. **Principle of the maximisation of the public interest and of distributive justice** whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socialy better off but also the least advantaged; and, in particular, the research subject themselves.

Principle of Institutional Arrangements whereby, there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.

Principle of public domain whereby, the research and any further research, experimentation or evaluation in response to,and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.

Principle of totality of responsibility whereby, the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment – including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use – so that, *inter alia*, the effect of the research or experiment is duly

monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

XII. **Principle of Compliance** whereby, there is a general and positive duty on all persons conducting, associated or connected with any research entailing the use of a human subject to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directions and guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with.

PART B

SPECIFIC PRINCIPLES

(a) Human Genetics Research

(b) Transplantation Research including Fetal Tissue Transplantation

(c) Clinical Evaluation of Drugs/Devices/ Vaccines/Herbal Remedies

(d) Epidemiological Research

(e) Assisted Reproductive Technologies

STATEMENT OF SPECIFIC PRINCIPLES ON HUMAN GENETICS RESEARCH

INTRODUCTION

In no other area of biomedical research there has been a greater concern for ethical issues than in the field of human genetics. While the advent of recombinant DNA technology has provided one of the most powerful tools in the hands of mankind to unravel the mysteries of the human genome, it has also led to a great deal of concern about our ability to handle the information so derived.

Human beings cannot be experimental animals in any field of research. The knowledge about human genes and genetic diseases prior to fifties was so poor that there was hardly any human genetic experimentation. Since then, and especially in the past decade, there has been a veritable explosion in knowledge which has culminated in gene therapy (the ultimate in thereapy for genetic diseases) and various other aspects of genetic engineering.Serious issues related to participation of human subjects in genetic research are raised , particularly when the intervention involves rights of human embryo and subjects who are not competent to give informed consent. Besides the Human Rights issues of dignity, autonomy, and justice, the Human Genome Project (HGP) has also precipitated an unprecedented concern for Intellectual Property Rights. Recent experiments on cloning sheep and monkeys bring human cloning into the realm of possibility, raising Ethical, Legal and Social Issues (ELSI) as important aspects of HGP. This calls for laying down of rules and regulations in a stepwise fashion with the least amount of ambiguity.Special guidelines are required to contain the potential harm without clamping a moratorium on research and service in this field.

PREAMBLE

Clinical Research in fields of Human genetics and human genome, including gene therapy, besides being subject to general ethical considerations of protection from harm and voluntariness of participation has following additional considerations which require special guidelines:-

1. The harm may not only be physical, but also psycho-social. Psychologically, the genetic information may produce anxiety and depression or damage familial relationship, which should be safeguarded. There is a likelihood of social stigmatisation and discrimination in employment, health and general insurance, which requires much greater care in recruiting subjects in the study, obtaining informed consent and maintaining confidentiality of research findings, than in any other area of research.

2. There is great importance of spoken word in medica genetics, since genetic counselling is akin to therapy i other fields. In that sense the 'word' is equivalent t drug/intervention in medical genetics. Written explanatio understandable to layman about the disease/interventions and outcome as also the implication of the informatio generated for progeny and family, has special place i clinical research in this field.

3. Genetic Counselling deals with the discussion on persona matters such as reproductive options, and the couple has t make choices which have far reaching social implications It, therefore, calls for special care which should b documented in research proposals carefully considered b Ethical review committees.

4. Genetic manipulations have consequences for the future, som of which are unknown. Hence, greater care towards potentia dangers is necessary.

5. There is greater likelihood of situations cropping up wher there is conflict of interest between an individual, an that of family and society at large. Careful guidelines ar needed to be evolved by the peers in the profession t tackle such situations. The professional societies should b called upon to actively participate in these activities.

6. The science of Medical Genetics is progressing very rapidly Therefore, there is need for frequent updating of an guidelines for research in this field. To meet thi challenge not only the guidelines should be flexible, bu there should also be a built-in mechanism to review th guidelines from time to time. The Ethical Review Commitee should have necessary expertise which include knowledge o latest developments. In areas of doubt open discussion shal be encouraged.

7. Concerned with the misuse of genetic tests, particularly fo the preselection of sex, the Government has enacted a la known as "The Prenatal Diagnostic Techniques (Regulation Prevention of Misuse) Act 1994". The provisions of this ac shall be followed by all researchers in this area (and suc other acts which may be passed in future).

8. These guidelines are not only for research on huma subjects, but are part and parcel of the clinical practic of Medical Genetics as well.

DEFINITIONS

Genetic material/Genome

Genetic material refers to the material made of DNA in eac cell of any organism. The DNA is divided into genes. Each gen contains the information required to produce on

polypeptide/protein needed by the organism.

Chromosome

The thread-like DNA in a cell is divided into several separate lengths. Each length forms a structure called a chromosome. There are two copies of each chromosome in every cell. Human cells contain 23 pairs of chromosomes.

Gene

A gene is a length of DNA that contains the information needed to make one polypeptide. For example, the beta globin gene contains the information needed to make the beta globin polypeptide found in the hemoglobin of red blood cells. More than one gene may be involved in making one protein, and more than one polypeptide may be formed from one gene as a result of alternate splicing.

Genetic Engineering

It is the process of changing the genetic material of an animal or an organism or a plant. The main method of genetically modifying the organism is by transgenesis.

Heterozygote

Each cell of an organism contains two copies of each gene. In a heterozygote, the two genes of a pair are different from each other.

Homozygote

Each cell of an organism contains two copies of each gene. In a homozygote, both copies of the gene are identical to each other.

Mutation

A process by which the DNA of an organism changes or mutates. In humans this can lead to disease such as thalassemia in which the mutation results in decreased production of beta or alpha globin. The mutant gene is passed down from a parent to the offspring and so the condition is inherited. In viruses, and other infectious organisms, mutations can lead to emergence of organisms with new characteristics. It can make them more virulent, or resistant to antibiotics thus increasing their infectivity.

Patent

A patent is a monopoly right, granted for a limited period, given to an inventor in return for the publication to the world at large of the details of an invention.

Recombination

A cross-over between two members of a pair of chromosome results in the formation of a recombined chromosome wherein a ne set of gene arrangement is created.

Transgenesis

This refers to the introduction of a foreign gene into a animal or other organisms. The transferred gene is called transgene.

Transplantation

Transplantation involves the removal of organs, tissue o cells from one organism and their implantation into anothe organism.

GENERAL PRINCIPLES

The 12 principles laid down under Statement on Genera Principles are common to all areas of biomedical research. Th specific issues are mentioned under relevant topics.

Review Committee in Human Genetics

All institutions where research is carried out on huma genetics should have an Ethical Review Committee with adeq'at expertise in the field. Scientific competence of th investigator and sound scientific methodology should be essentia prerequisites for genetic research. It includes appropriat training, planning, pilot and field testing of the protocols containment where necessary and quality control of laborator techniques.

Informed Consent

For all biogenetic research involving human subjects the investigator must obtain the informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the proxy consent of a properly authorized representative/legal guardian should be taken.

Research involving children

Before undertaking research involving children, the investigator must ensure that :

- children will not be involved in research that might be carried out equally with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal guardian of each child has given proxy

consent;

- the consent of each child has been obtained to the extent of the child's capabilities;

- the child's refusal to participate in research must always be respected unless according to the research protocol the child would receive therapy for which there is no medically acceptable alternative;

- the risk presented by interventions not intended to benefit the individual child-subject is low and commensurate with the importance of the knowledge to be gained; and

- interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child-subject as any available alternative

Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information, in language that he or she is capable of understanding. The communication should not only be scientifically accurate but should be sensitive to their social and cultural context:

- that each individual is invited to participate as a subject in research. The aims and methods of the research should be fully explained to the concerned individual.

- the expected duration of the subject's participation;

- the benefits that might reasonably be expected to result to the subject or to others as an outcome of the research;

- any foreseeable risks or discomfort to the subject, associated with participation in the research;

- any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment being tested;

- the extent to which confidentiality of records in which the subject is identified will be maintained;

- the extent of the investigator's responsibility, if any, to provide medical services to the subject for any unexpected injury/illness resulting from the research free of charge;

- research subjects who suffer physical injury as a result of their participation are entitled to medical care as an institutional responsibility;

- that the individual is free to refuse to participate and

will be free to withdraw from the research at any ti without penalty or loss of benefits to which he or she wou otherwise be entitled. All possible means of coercion direct or indirect rewards for participation should scrupulously avoided.

Equitable distribution of burdens and benefits

Individuals or communities to be invited to be subjects genetic research should be selected in such a way that t burdens and benefits of the research will be equitab distributed. Special justification is required for inviti vulnerable individuals (prisoners, mentally retarded subject medical students, nurses, subordinates, employees etc.) and they are selected, the means of protecting their rights ar wishes must be strictly applied. Persons who are economically c socially disadvantaged should not be used as research subjects t benefit those who are financially better off.

Pregnant or Nursing women as research subject

Pregnant or nursing women should in no circumstances be th subject of genetic research unless the research carries no mor than minimal risk to the fetus or nursing infant and the objec of the research is to obtain new knowledge about the fetus pregnancy and lactation. As a general rule, pregnant or nursin women should not be subjects of any Clinical Trials except suc trials as are designed to protect or advance the health o pregnant or nursing women or fetuses or nursing infants, and fo which women who are not pregnant or nursing would not be suitable subjects.

Confidentiality of data

The investigator must establish secure safeguards for the confidentiality of the research data. Subjects should be told of the limits to the investigator's ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality. When **commercial companies** are involved in research, it is necessary to protect researchers and subjects from possible coercion/inducement to participate in the study.

Academic institutions conducting research in alliance with industries/commercial companies require a strong review to probe possible conflicts of interest between scientific responsibilites of researchers and business interests (e.g. ownership or part-ownership of a company developing a new product). In cases where the review board determines that a conflict of interest may damage the scientific integrity of a project or cause harm to research participants, the board should advise accordingly. Institutions need self-regulatory processes to monitor, prevent and resolve such conflicts of interest.

Prospective participants in research should also be

informed of the sponsorship of research, so that they can be aware of the potential for conflicts of interest and commercial aspects of the research.

Undue inducement through compensation for individual participants, families and populations should be prohibited. This prohibition, however, does not include agreements with individuals, families, groups, communities or populations that foresee technology transfer, local training, joint ventures, provision of health care or of information infrastructures, reimbursement costs of travel and loss of wages and the possible use of a percentage of any royalties for humanitarian purposes.

SPECIFIC PRINCIPLES

I. HUMAN GENETIC DISEASES/DISORDERS

Pedigree Studies

These involve obtaining history of other members of the family of the proband under investigations. It may reveal information about the likelihood that individual members of the family either are carriers of genetic defects or may be affected by the disease.

Special privacy and confidentiality concerns arise in genetic family studies because of the special relationship between the participants. It should be kept in mind that within families each person is an individual who deserves to keep the information about himself or herself confidential. **Family members are not entitled to know each other's diagnosis.** Before revealing medical or personal information about individuals to other family members, investigator must obtain the consent of the individual. In our country revealing the information that the wife has balanced chromosomal translocation (leading to recurrent abortions or a genetic syndrome in her child) or that she is a carrier of a single gene *i.e.* 'X' linked or recessive disease, may lead to the husband asking for a divorce inspite of the fact that in some of the cases, the husband himself may be a carrier of a recessive disorder. While general principles of Counselling require the presence of both the spouses, necessary care must be taken not to end up in breaking the families.

Subject recruitment

The familial nature of the research cohorts involved in pedigree studies can pose a challenge for ensuring that recruitment procedures are free of elements that unduly influence the decision to participate. The very nature of the research exerts pressure on family members to take part, because the more complete the pedigree, the more reliable the resulting information will be. Problems which could arise when -

1. Revealing who else in the family agreed to participate may lead to breach of confidentiality.

2. A proband is used for revealing his personal interes he/she may put undue pressure on relatives to enroll in th study.

3. Direct recruitment (by telephone calls) may however be see as an invasion of privacy by family members.

4. Contact through personal physicians may imply that thei health care will be compromised if they do not agree t participate.

Defining risks and benefits

Potential risks and benefits should be discussed thoroughl with prospective subjects. In genetic research, the primar risks outside of gene therapy are psychosocial rather tha physical.

Adequate counselling should be given to subjects on th meaning of the genetic information they receive. Geneti counselling should be done by persons qualified and experience in communicating the meaning of genetic information.

II. GENETIC SCREENING

Definition : A search in a population to identify individual who may have, or be susceptible to, a serious genetic disease o who, though not at risk themselves, are gene carriers and thu may be at risk of having children with a particular genetic disease.

Depending on the nature of the genetic defect that is identified and its pattern of inheritance, siblings and other blood relations as well as existing and future offsprings may be affected. Thus the status of genetic information raises, ethical questions that differ significantly, from the normal rules and standards applied to the handling of personal medical records. Adequately informed consent is therefore essential. Those being screened are entitled to receive sufficient information in a way that -

i) they can understand what is proposed to be done

ii) they must be made aware of any substantial risk

iii) they must be given time to decide whether or not to agree to what is proposed and they must be free to withdraw from the investigation at any time.

The Disorder to be screened and its inheritance pattern should be explained as also the reliability of the screening test, the procedure for informing individuals of the results, what will be done with the samples, information about the implication of a positive screening test (abnormal) and a

warning to pregnant women that genetic screening may reveal unexpected and awkward information, for example about paternity.

Confidentiality should be maintained in handling of the results with an emphasis on the responsibility of individuals with a positive (abnormal) result to inform partners and family members.It should be emphasised that consent for screening or a subsequent confirmatory test does not imply consent to any specific treatment or to the termination of a pregnancy.

General guidelines have to be followed for vulnerable individuals i.e minors, mentally ill, prisoners, students, subordinates, people who do not speak the language of the investigator etc.

Genetic counselling should be readily available for those being screened. Confidentiality of medical information is protected by law but this is not absolute. Information may be disclosed where it is in the public interest to do so.

Screening New Borns : Screening of new borns should be allowed to detect only those genetic diseases like phenylketonuria where the serious effects of the disease could be prevented by a special diet or treatment . The same applies to investigations to detect genetic, chromosomal, metabolic abnormalities, etc. if general principles mentioned earlier are followed. The other diseases can be screened as and when interventions/therapy is made available in future.

Prenatal testing : It is aimed at detecting the presence of genetic or chromosomal abnormalities in fetuses. Examination of the genetic nake up of the fetus is done through amniocentesis, chorionic villi sampling, placentocentesis, cordocentesis (blood sampling from the umbilical cord) and skin and other biopsies,and also examination of blood samples from the mother. Embryoscopy may be used to detect external malformations.

Anonymous testing: Researchers may conduct anonymous testing or screening on the general population in order to establish the prevalence of genetic anomalies and deleterious genes.This is now possible by PCR(polymerase chain reaction) amplification which uses a single blood spot or a small sample of blood for multiple tests. Blood spots collected in screening newborns for treatable disorders could be used to collect epidemiologic information about genetic predispositions to disorders of late onset. In cases where the information derived from stored specimens might be useful to individuals, the code of anonymity may be broken. All the criteria mentioned in the general principles like informed consent, confidentiality etc. should be observed.

Genetic Registers : Computer based genetic registers are subject to Data Protection Act but there is need for additional safeguards for all genetic registers, including storage of information in a safe place and manner, restriction of access to only those specifically responsible for the register, and the

removal of identifying information when data are used fo
research purposes.

The practice of genetic screening in employment: It may be don
only when justified and in the interest of the employees i.e
Sickle Cell Disease screening for those in aviation industry wh
are likely to be exposed to atypical atmospheric conditions. A
employer may use genetic screening procedures with the consent o
entrants (This issue is not decided in many countries). This
screening may be only for a disorder which might be harmful t
the employee or any disorder which may jeopardise other people
in the relevant function or job. (Any possibility of direct o
indirect threat to the job should be scrupulously avoided.)

Subject to prior consultation with workplace
representatives, and with appropriate Health authorities, it is
recommended that genetic screening of employees for increased
occupational risks ought only to be contemplated where-

i) there is strong evidence of a clear connection between the
working environment and the development of the condition for
which genetic screening is to be conducted;

ii) the condition in question is one which seriously endangers
the health of the employee or is one in which an affected
employee is likely to present a serious danger to third
parties;

iii) the condition is one for which the dangers cannot be
eliminated or significantly reduced by reasonable measures
taken by the employer to modify or respond to the
environmental risks.

Insurance companies should adhere to the current policy of not
requiring any genetic tests as a prerequisite of obtaining
insurance. This is forbidden by law in some countries .e.g. USA.

Public policy & genetic screening

There is a very great need for improving public awareness
and understanding of human genetics. There should be a central
coordination and monitoring mechanism for a genetic screening
programme in the interest of the public, the majority of which
have little knowledge of genetics.

III. THERAPEUTIC APPROACHES INCLUSIVE OF GENE THERAPY

Genetic disorders which require nutritional replacement
therapy like phenylketonuria do not pose any ethical problem.
Replacement with animal products should follow the rules as
stipulated for other diseases.

Gene Therapy

The goal of human genetic research is to alleviate human

suffering. Gene therapy is a proper and logical part of this effort. Gene therapy should be subject to all the ethical codes that apply to research involving patients.

i) Somatic gene therapy is the only method out of the four types of Genetic Engineering that may be allowed for the purpose of preventing or treating a serious disease when it is an ethical therapeutic option. It should be restricted to the alleviation of disease(life threatening or seriously disabling genetic disease) in individual patients and should not be permitted to change normal human traits.

Safety should be ensured especially because of the possibility of unpredicted consequences of gene insertion. It should provide for long term surveillance. Informed consent must be taken especially regarding uncertainities about outcome, as children could be candidates for therapy.

ii) Germ Line therapy should not be attempted at present because there is insufficient knowledge to evaluate the risk to future generation. Unpredictable outcome is a more valid reason than fear of unscrupulous people in power acquiring undue powers.

iii) Enhancement Genetic Engineering for altering human traits should not be attempted as we possess insufficient information at present to understand the effects of attempts to alter/enhance the genetic machinery of humans.

It is not wise, safe or ethical for parents to give for example growth hormone to their normal offspring in order to produce very large football or basketball players. Similarly it would be unethical to use genetic engineering for improvement of intelligence, memory etc even if specific gene/genes are identified in future.

iv) Eugenic Genetic Engineering for personality, character, formation of body organs, fertility, intelligence and physical, mental and emotional characteristics are enormously complex. Dozens, perhaps hundreds, of unknown genes that interact in totally unknown ways, probably contribute to each such trait. Environmental influences also interact with these genetic backgrounds in poorly understood ways. The concept of remaking a human i.e. eugenic genetic engineering is not realistic and has grave risks of this being misused by unscrupulous people in power. This should not be allowed.

IV. ISSUES RELATED TO NATIONAL AND INTERNATIONAL COLLABORATIVE RESEARCH

It is important that all research with human subjects adequately protect the rights and welfare of the subjects. All human genetic research in India will be subject to guidelines of the funding agencies and rules and regulations laid down by the Govt. of India if it were conducted wholly within the country.

International collaborative projects should not only follow the guidelines for collaboration but make sure that the investigations should follow the guidelines given by the financial agencies/national bodies especially with regard to ethical guidelines. This includes international standards, declaration of Helsinki or Nuremberg code. Written descriptions of the specific procedural implementation of such policies that have been adopted by the collaborating institutions in their own countries are required.

Investigators should be very clear as to which part of the project will be done in a foreign country and also what specific sample will be taken out of the country for the project. It should be strictly forbidden to utilise the sample for any other purpose than for the specific purpose mutually agreed to and sanctioned by the appropriate authority. To be specific no DNA from human subjects should be sent out of the country unless it follows the procedure and guidelines laid down by the Indian Council of Medical Research/Government of India. In the event of failure of agreement the guidelines of the country (India) shall prevail.

Commercialization

The human genome in its natural state is not subject to private, national or transnational ownership by claim of right, patent or otherwise. Intellectual property based upon the human genome may be patented or otherwise recognised in accordance with national laws and international treaties. Question of patenting DNA should be clearly stated. Who should benefit should also be specified. The percentage benefit to be given/received should be mentioned in writing through a carefully drawn Memorandum of Understanding.

V. HUMAN GENOME DIVERSITY

Deptt. of Biotechnology, Ministry of Science & Technology has brought out a document on genomic diversity which envisages the following -

(i) To support a network of laboratories in India for studying genomic diversities of anthropologically well-defined populations following a uniform set of protocols for collecting information, and screening a uniform set of genomic markers by inviting and implementing project proposals under the framework of this programme.

(ii) To establish a national repository of biological samples (DNA, cell lines etc.) with appropriate safeguards, regulations and monitoring.

(iii) To establish and integrate regional and national statistical databases comprising genomic, epidemiological, cultural and linguistic data on Indian population.

The biological tools, materials and analysis of DNA samples will be carried out by Indian scientists in Indian laboratories. The biological samples collected under this programme, as well as the data generated, have a variety of ethical, legal and commercial implications.

Scientists involved in this will follow appropriate ethical protocols and respect the rights and sensitivities of the participating individuals and populations. The relevant issues pertain to: i) the mechanism for collection of samples, ii) who can have access to the samples and for what purposes, iii) who owns the DNA; and iv) to establish measures for quality control of the laboratories.

VI. RESEARCH RELATED TO DNA BANKING

Primary use

DNA samples should not leave the country without following the guidelines evolved by the Govt. of India with clear undertaking that it should not be used for any other purpose other than the original intent for collection.

Secondary use

In every case where a new study proposes to use samples collected for a previously conducted study, the ethical committee should consider, whether the consent given for the earlier study also applies to the new study, whether the objectives of the new study diverge significantly from the purpose of the original protocol, and whether fresh consent has been obtained when the new study depends on the familial identifiability of the samples.

Internationally the accepted norm is to obtain fresh consent for any secondary use. The consequences of DNA diagnosis for which no treatment is available or for conditions menifesting late in life *e.g.* breast cancer, Alzheimer's *etc.* should be seriously considered before embarking on DNA diagnosis.

VII. DNA DIAGNOSIS

The general principles of informed consent, confidentiality and other criteria used for any investigation in genetics should be followed.

Preimplantation DNA diagnosis- As there are various types of investigations in this area this should be reviewed by an ethical committee.

In children - Parents are advised not to get the diagnosis done especially in cases like Huntington's disease till the child reaches the age of proper "consent" to the test.

In adults, the vulnerable population should be kept in mind while following the general principles. Unless appropriate counselling

services are available DNA diagnosis is fraught with gr
psycho-social implications.

VIII. ASSISTED REPRODUCTIVE TECHNIQUES

Definition

Any fertilization involving human sperm and ova that occ
outside the human body. There is no objection ethically as
the moment for IVF or any other related procedure for conduct
research or for clinical applications.

"Informed consent" should include information regarding
of "spare" embryos. It should be made clear whether embryos t
are not used for transfer could or could not be used for resea
purposes or implanted in another woman's womb, or "preserv
for use at a later date or destroyed. Investigators sho
ensure that participants are informed and consent is taken
writing.

Investigators should clarify the ownership of the embry
whether they belong to the biological mother or the laboratory
Abortions should never be encouraged for research purposes.

A **National Advisory Board for ethics in reproduction** shou
be constituted which can evaluate research proposals in th
area.

Fetuses as research subjects - Research involving human fetus
raises special concerns. The fetus has a unique and inextricab
relationship to the mother. It cannot consent to be a resear
subject. The fetus may also be an indirect subject of resear
when women, who may be pregnant, participate in the research.

**Respect for safeguarding of personal and parental reproducti
choices** - Reproductive decisions should be the province of tho
who will be directly responsible for the biological and soci
aspects of child bearing and child rearing. Usually this mea
the family. However, when a couple is unable to reach
agreement, the mother should have the final authority
decision.

Women have a special position as care givers for childr
with disabilities. Since the bulk of care falls upon the woma
she should make the final decision among reproductive options
without coercion from her partner, her doctor, or the law
Choice is more than the absence of legal prohibition or coercion
Choice should include the economic and social ability to act upo
a decision, including disability. There should be a positiv
right to affordable genetic services, safe abortion and medicall
indicated care for children with disabilities.

Cloning -

(i) through Nuclear transplantation : This seems to be

possibility in the near future as sheep and monkeys have already been cloned. The ethical implications need not be expanded. **Research on human cloning definitely should be forbidden by law.**

(ii) **through embryo splitting:** Embryo splitting is ethically acceptable provided that the resulting embryos are not damaged or destroyed in the process. There are many issues involved here which require separate discussion.

a. It is ethically acceptable to use embryo splitting to produce embryos for simultaneous implantation in the same woman. (Not more than **four** embryos shall be produced from a single embryo) and to cryopreserve embryos resulting from embryo splitting for transfer and implantation in a subsequent IVF cycle, should an initial IVF cycle using split embryos prove unsuccessful.

b. It is unacceptable to split embryo and retain them in a cryopreserved state for the sole purpose of :

- providing an adult with an identical twin to raise as his or her own child
- having a large family of genetically identical children
- retaining a "back-up" embryo as a potential replacement for a child who dies
- retaining a "back-up" embryo as a potential organ or tissue donor for an identical twin already born
- retaining a "back-up" embryo as a potential source of fetal tissue, organs or ovaries
- donation to others
- sale to others.

Whether it is ethically acceptable to split embryos for the specific purpose of allowing preimplanation diagnosis on one of the resulting embryos if that embryo would be damaged in the process is debatable.

Research involving human embryos: This should be permitted with appropriate safeguards. Studies of "normal" embryos will lead to understanding the process of fertilization, which cannot be entirely accomplished by animal research. Additionally, studies of "abnormal" embryos are a potential source of scientific information at the molecular level about the origins and development of genetic disorders, malformations and pediatric cancers. To understand the natural history of some genetic diseases, it will be necessary to obtain sperm and eggs from parents who are at higher risk to transmit these conditions to offspring, and to study the genetic mechanisms involved compared

to those in "normal" embryos. Thus, restricting embryo resea
only to spare embryos donated after infertility treatment w
not be sufficient.

The embryo does not have the same moral status as infant
child, although it deserves respect and moral consideration a
developing form of human life. This judgement is based on th
characteristics of pre-implantation embryos; absence
developmental individuation, no possibility of sentie
(feeling) and a high rate of natural mortality at this sta
Harm cannot be done to such an organism until the capacity
sentience has been established. From this perspective there i
clear difference between the moral status of living children
embryos. It is possible to damage an embryo in research.
damage would become "harmful" in the moral sense only if
embryo was transferred to a human uterus and a future senti
person was harmed by the damage once done to the embryo. T
possibility can be avoided by regulations forbidding the trans
of any embryo that has been involved in research to a hu
uterus.

Respect for embryo can be shown by (1) accepting limits
what can be done in embryo research, (2) committing to
inter-disciplinary process of peer group review of plan
research, and (3) carrying out an informed consent process
gamete and embryo donors. Further, respect for the embry
limited moral status can be shown by careful regulation of
conditions of research, safeguards against commerc
exploitation of embryo research, and limiting the time wit
which research can be done to **14 days**. This last restriction
in keeping with the policy in several nations that per
research with embryos (Australia, Great Britain, American Coll
of Obstetrics and Gynaecology 1986; Human Fertilization
Embryology Authority, 1993; Royal Commission on New Reproduct
Technologies, 1993) until the developmental stage when
"primitive streak" appears. At this time, the development
nervous system begins and the embryo begins to become a disti
individual.

Adoption: Adopted children or children born from use of do
gametes, and their social parents, should have the right to k
whatever medical or genetic information about the genetic pare
that may be relevant to the child's health. Genetic testing
adopted children or children awaiting adoption should fall un
the same guidelines as testing of biological children.

IX. HUMAN GENOME PROJECT (HGP)

The human genome project (HGP) is an international resea
effort, the goal of which is to analyse the structure of hu
DNA and to determine the locations of the estimated 1,00,
genes. Another component of the programme is to analyse the
of a set of non-human model organisms to provide comparat
information that is essential for understanding how the hu
genome functions. The project began formally in 1990.

The investigators have been able to identify and isolate human genes particularly those associated with diseases. The project has the potential for profoundly altering our approach to medical care from one of treatment of advanced disease to prevention based on the identification of individuals at risk. HGP is arguably the single most important organised research project in the history of biomedicine.

Ethical considerations

Implications of using this genetic knowledge pose a number of questions for -

1) individual and families - whether to participate in testing, with whom to share the results, and how to act on them

2) health professionals - when to offer testing, how to ensure its quality, how to interpret the results and to whom to disclose information

3) employers, insurers, the courts and other social institutions - the relative value of genetic information to the decisions they must make about individuals

4) for governments - about how to regulate the production, and use of genetic tests and the information they provide and how to provide access to testing and counselling services for society

5) for society - how to improve public understanding of science and its social implications and increase participation of the public in science policy making.

X. RESEARCHER'S RELATIONS WITH THE MEDIA AND PUBLICATION PRACTICES

Researchers have a responsibility to make sure that the public is accurately informed about results without raising false hopes or expectations. Researchers should take care to avoid talking with journalists or reporters about preliminary findings. Sometimes the media report potentially promising research that subsequently cannot be validated. Sometimes the media report research on animals in such a way that the public thinks that the step to treatment for humans is an easy one. Retractions almost never appear in the popular press or on television. Therefore it is important to avoid premature reports. The best safeguard against inaccurate reporting is for the researcher to require, as a condition for talking with the media, that the reporter supply a full written rather than oral version of what will be reported, so that the researcher can make necessary corrections.

Investigators publication plans should not threaten the privacy or confidentiality of subjects (publication of pedigrees can easily result in the identification of studying

participants). It is recommended that consent for the publicatio shall be obtained separately rather than as part of the conse to participation in research or treatment.

XI. GUIDELINES ON ETHICAL ISSUES FOR PROFESSIONALS AN PRACTITIONERS OF GENETICS IN THE FIELD OF HUMAN GENETICS

General ethical guidelines in medical genetics for healt workers and public are outlined. Respect for person include informed consent, right to referral, full disclosure, protectio of confidentiality and respect for children and adolescents i the context of genetic testing.

a) **Access to genetics services** - Access to genetics service should not depend upon social class or ability to pay Whatever services exist in a nation should be availabl equally to everyone. Genetic services should be provide first to those whose need for them is greatest. Hence there is a great need to set up genetic centres fo counselling as well as therapy where available.

b) **Non-directive counselling** - Genetic counselling should b non-directive i.e. the couple should be explained th various options available, while the final choice should b left to the couple. Illiterate subjects with no or poo understanding of scientific facts may be told what othe persons in their situation may opt to do.

c) **Voluntary approach** - It is essential to ensure that th individual voluntarily approaches genetic services includin genetic counselling, screening for susceptibility to commo diseases or to occupationally-related diseases presymptomatic testing, testing children, and prenata diagnosis. Persons who choose or refuse genetic service should not be the object of discrimination o stigmatization. Persons who choose or refuse geneti testing or services should not be penalized in terms o health care, employment, or insurance.

The only exception to the rule of voluntary screenin should be newborns, if, and only if, early treatment i available that would benefit the newborn. Therefore, th government may mandate screening for newborns who would b harmed by the absence of prompt treatment. When this i done the government would have the ethical obligation t provide prompt, affordable treatment for the disorders fo which they screen. Otherwise the screening would be i vain.

d) **Disclosure of information** - There should be full disclosur of clinically relevant information to patients Professionals should disclose all test results relevant t an individual's own health or the health of a fetus including results indicative of any genetic condition, eve if the professional regards the condition as not serious

Those who will bear and rear the child should decide, after receiving full and unbiased information, about the effects of the conditions on their family and their socio-cultural situation. Test results should be disclosed even if ambiguous or conflicting. New or controversial interpretations of test results should also be disclosed. Test results without direct relevance to health (e.g. nonpaternity, fetal sex in the absence of X-linked disorders) may be withheld if this appears necessary to protect a vulnerable party. Disclosure includes the duty to recontact individuals or families if new developments arise that are relevant to health.

e) **Duties to family members** - In genetics, the true patient is a family with a shared genetic heritage. Family members have a moral obligation to share genetic information with each other. If children are intended, individuals should share information with their partners. Individuals have a duty to inform other family members who may be at high risk. If an individual will not do so, the medical geneticist may issue a general warning to family members, but without revealing information about the affected individual. Preserving patient confidentiality is a well-known duty in medicine. This duty is mitigated if it conflicts with another well-known duty, preventing harm to other parties.

f) **Protection of privacy from institutional third parties** - Medical geneticists should recognize the potential for harm when institutions are allowed access to genetic information about individuals, even with the individual's consent. Therefore, such institutions should not have access to such data and should not be permitted to require genetic tests.

g) **Prenatal diagnosis** - This should be performed only for reasons relevant to the health of the fetus or the mother. Prenatal diagnosis should not be performed solely to select the sex of the child (in the absence of an X-linked disorder). Sex selection, whether for male or female, denigrates the fundamental personhood of those already born, and has the power to harm societies by unbalancing sex ratios. The potential harm to large groups of people outweighs any immediate benefits to individuals or families. The Government of India has already passed legislation banning diagnosis of sex for non-medical reasons.

Prenatal diagnosis can be used to prepare parents for the birth of a child with a disability. Therefore, prenatal diagnosis should be available to such parents who request it but oppose abortion, provided that they understand and are willing to accept the risks to the fetus.

In some cases, prenatal diagnosis may be performed to protect the health of the mother. These include clinically confirmed cases of morbid anxiety or situations where prenatal paternity testing would benefit the mother's mental

prenatal paternity testing would benefit the mother's menta
health (e.g. if rape occurred while a couple was trying t
conceive).

Professionals should recognize the human and economi
costs involved in prenatal diagnosis and should limit it
use to situations where there is a clear benefit.

RESOURCE MATERIAL

1. The human genome project & the future of Medicine
   Mark S Guyer & Francis S Collins
   Human Genome Project, Guyer & Collins, Vol 147, Nov 1993,
   P 1143-1151.

2. Nuffield Council on Bioethics U.K.
   Genetic screening & ethical issues

3. Nuffield Council on Bioethics, UK
   Human tissues Ethical & legal issues

4. Safeguards for Gene Therapy
   Notice Board, The Lancet, Vol.339, Jan 25, 1992 Page 238

5. The Prenatal Diagnostic Techniques Act,India (1994).

6. DBT Guidelines for Gene Therapy,India (1996)

7. Guidelines for Exchange of Human Biological Material for
   Biomedical Research Purposes,Ministry of Health & family
   Welfare,India (1997).

ETHICAL GUIDELINES FOR RESEARCH IN TRANSPLANTATION INCLUDING FETAL TISSUE TRANSPLANTATION

INTRODUCTION

The practice of transplantation is in its infancy in India. The exceedingly high cost restricts its application, and also reduces the interest in research into this field. The same reason makes it imperative that Indian scientists should devise means of reducing the cost and improving the success rate, to make it feasible to increase the number of Indians who can benefit by this treatment. At present the protocols devised in the West are followed which are not necessarily ideal. The ethical principles of research in human subjects have been well enunciated in the Declaration of Helsinki adopted by the World Medical Association in 1964, and amended in 1975, 1983, and 1989. Transplantation, however, raises some peculiar aspects, and these will have to be weighed in that light. The problem has been considered with special reference to the following points:-

I. Recommendations on existing legislation
II. Recommendations on Institutional Review Committees
III. Transplants from live or cadaver donors
IV. Embryonic and foetal tissue and organ transplantation
V. Xeno-transplantation
VI. Transplantation for cosmetic purposes.

I. RECOMMENDATIONS ON EXISTING LEGISLATIONS

This committee strongly recommends an amendment of the existing *'Transplantation of Human Organs Act, 1994'* with *'Transplantation of Human Organs Rules, 1995'* to bring within its ambit transplantation research, including transplantation of foetal tissue or organs, since the existing Act does not permit this in clinical practice and is silent on research on transplantation.

A. THE SECTION ON BRAIN DEATH AND THE ACCEPTANCE OF BRAIN DEATH AS THE LEGALLY ACCEPTED DEFINITION OF DEATH MUST BE DE-LINKED FROM ORGAN TRANSPLANTATION AND MADE UNIVERSALLY APPLICABLE.

The diagnosis of brain death, as it stands under the Act at present, is legally valid only when the concerned patient is a donor of organ(s). This has led to the following anomaly:

- When the patient is a potential donor of organ(s), once a diagnosis of brain death has been made and the consent of the legal heirs for organ donation obtained, the heart, liver, kidneys, pancreas and any other vital organ can be removed for transplantation.

- When, however, for some reason, the patient is not donor of organ(s), life support systems cannot be tak off even after the diagnosis of brain death has be made as specified in the Act. This results prolongation of agony for the relatives, unnecessa increase in costs and denial of life support syste such as ventilators to other patients whose lives mig be saved by them.

B. EXCLUDE THE SPOUSE FROM THE CATEGORY OF RELATED DONORS ORGANS AS THERE IS NO GENETIC SIMILARITY BETWEEN THE SPOU AND THE RECIPIENT.

The organ taken from the spouse is as liable to rejecti as is that from any other unrelated individual.

C. BRING TRANSPLANTATION RESEARCH INCLUDING TRANSPLANTATION FOETAL TISSUE OR ORGANS WITHIN THE AMBIT OF THIS ACT.

The existing Act does not permit the use of fetal tissues organs as transplants in clinical practice and does n include the area of research on transplantation.

II. RECOMMENDATIONS ON INSTITUTIONAL REVIEW COMMITTEES

Scientific Committee

1. Each research proposal should initially be processed by th local scientific committee. After approval of the scientifi committee has been obtained, the proposal should b scrutinised by the local ethics committee. Special attentio should be paid to all aspects concerning safety an efficacy.

2. Strict criteria are recommended for the formation an function of **scientific committees** in institutions proposin to carry out research on organ transplantation. Suc committees must be composed of at least : **two physicians** an **two surgeons** competent in the field of transplantation o the tissues or organs to be used; an **immunologist** wit special interest in tissue-typing and transplantation; **microbiologist**; a **biostatistician**; a **member-secretary** wh shall be responsible for all administrative matter pertaining to the ethics committee, including th preservation of minutes of each meeting and all othe relevant documents. At least two members of the scientifi committee shall be from **outside** the institution.

Ethics Committee

1. We recommend strict criteria for the formation and function of ethics committees in institutions proposing to carry out research on organ transplantation. Such committees must be

composed of at least **two physicians**, one of whom is in charge of the intensive care unit that will look after recipients of organ and tissue transplantation; **two basic scientists**, one of whom has experience in clinically applied research; **two senior nurses**, one of whom has experience of taking care of recipients of organ and tissue transplantation; **four lay persons**, one of whom is a lawyer, the others being individuals with competence in ethical and social issues (philosopher, social worker, journalist); **an administrator; a member-secretary** who shall be responsible for all administrative matters pertaining to the ethics committee, including the preservation of minutes of each meeting and all other relevant documents. At least three of these members must be **women** to ensure attention to issues concerning this sex.

2. These committees shall follow national or international guidelines on research laid down by such agencies as the Indian Council of Medical Research, the National Institutes of Health, USA, *etc.* When doubt exists, the committees shall seek the opinion of the Indian Council of Medical Research, which shall be binding.

3. These committees must meet regularly, maintain detailed records on all proposals brought before them and their decisions on each project with reasons for acceptance or rejection, reports on follow-up observations on each project sanctioned, the final report on each project and a copy of each publication resulting from each project.

4. These committees must ensure that all records pertaining to each research project sanctioned are carefully maintained under their supervision for a minimum period of five years after the completion of the project. It shall be the joint responsibility of the ethics committee and the principal research officer/s to produce such records on demand by any authorised individual or agency.

5. These committees must be certified soon after their establishment by a Government agency or agencies according to procedures laid down by the Ministry of Health and Family Welfare. This certificate must be renewed from time to time as specified by the Ministry.

III. TRANSPLANTS FROM LIVE OR CADAVER DONORS

DEFINITIONS

Cadaver: A dead body. For purposes of this document, the term refers to a dead human body.

Death: This was originally defined as entire and continuous cessation of respiration and circulation. It has since been recognised that the heart could continue beating for a time, even

for days, though the brain lacked the ability to maintain respiration and sustain life. Death of the brain stem, also called brain death, has since been recognised internationally, and in the 'Indian Transplantation of Human Organs Act', 1994.

Brain death: This is as specified in 'Transplantation of Human Organs Act, 1994' with ' Transplantation of Human Organs Rules, 1995. The salient features are described below:-

Entire, permanent, and irreversible cessation of functions of the brain stem - this is synonymous with brain-stem death, since the centres for the control of such essential body functions as consciousness, respiration, and blood pressure are situated within the brain stem. In many countries strict criteria for diagnosis of brain death have been established. These include the presence of deep coma, the absence of any brain-stem functions such as spontaneous respiration, pupillary reactions, eye movements, and gag and cough reflexes, and the exclusion of low body temperature and drugs as relevant to the comatose state. The EEG is a useful (but not essential) confirmatory test. Brain death is when ' Damage is judged "irremediable" based on its context, the passage of time, and the failure of all attempts to remedy it. Secondly, all possible causes of reversible brain-stem dysfunction, such as hypothermia, drug intoxication, or severe metabolic upset, must be excluded. Finally,the absence of all brain-stem reflexes must be demonstrated, and the fact that the patient cannot breathe, however strong the stimulus, must be confirmed.

When testing the brain-stem reflexes, the following normal responses must be looked for: (1) constriction of the pupils in response to light, (2) blinking in response to stimulation of the cornea, (3) grimacing in response to firm pressure applied just above the eye socket, (4) movements of the eyes in response to the ears being flushed with ice water, and (5) coughing or gagging in response to a suction catheter being passed down the airway. All responses have to be absent on at least two occasions with an interval of six hours between them. Apnoea, which also must be confirmed twice, is assessed by disconnecting the patient from the ventilator. (Prior to this test, the patient is fully oxygenated by administering 100% oxygen for several minutes. This precaution ensures that the patient will not suffer serious oxygen deprivation while disconnected from the ventilator.) The purpose of this test is to establish the total absence of any inspiratory effort as the carbon dioxide concentration in the blood (the normal stimulus to breathing) reaches more than sufficient levels to stimulate any respiratory centre cells that may still be alive.

Guidelines on Live donor transplants

1. Donation from a live donor should be restricted to renewable tissues like bone marrow, or to a paired organ whose removal will not greatly alter physiological functions, like the kidney. Since the removal of an eye will compromise

binocular vision and produce disfigurement, it should not be permitted in a live donor.

2. Surgery on the donor inflicts bodily harm on him or her, the extenuating circumstances being the saving of another human life. It is imperative that no risk be imposed on the donor beyond that inherent in surgery and the loss of a vital organ. Any manner of experimentation, though it may be intended to improve the survival of the graft, should be prohibited if there is the slightest extra risk to the donor. Examples are pre-treatment of the donor with immunosuppressives or anticoagulants.

3. Every such research project should be preceded by careful assessment of predictable risks and compared to foreseeable benefits and improvement in the success rate of transplantation.

4. The interests of the donor should always take priority over those of the recipient of the transplant.

5. In view of the risk involved, the voluntary consent of the donor is absolutely essential. Further, the donor should be informed of all possible risks in a manner easily understood by him, before his consent is taken.

6. It follows that the donor should have the legal capacity to give consent; should be in a position to exercise free power of choice,without the slightest element of force, duress, or coercion; and should have sufficient knowledge and comprehension of the subject to be able to make a decision with full understanding of the consequences. Children and mentally incompetent adults as also individuals with restricted autonomy should not be used as organ donors or as subjects for such experiments.

7. Since the experiment would have consequences for the recipient too, the donor must be fully informed of the nature of the procedures and the possible effects on the recipient, before consent is taken.

8. The responsibility of providing the above information to the donor, and of making sure that he/she understands fully the implications of what is to be done and what he or she consents to, rests entirely on the individual who directs the research project.

9. The experiment should be such as to yield fruitful results for the overall good of the donee without any risk to the life of the donor. The experiment should be undertaken only if there is no other method available of finding the answer to the question raised. Research should also be aimed at developing means that will benefit the donor.

10. The experiment should be so planned and conducted as to

avoid all unnecessary risks to the donor, to the organ to b transplanted, and to the recipient of the organ.

11. Proper precautions should be taken and adequate facilitie should be available to protect the donor from the mos remote possibility of harm.

12. The donor should be at liberty to withdraw from th experiment and to abrogate the consent given earlier, wit no requirement to offer any explanation of the reasons fo his or her doing so.

13. If at any time during the course of the experiment the investigator comes to know that there is risk to the dono or to the recipient as a result of the procedure, it is hi or her responsibility to terminate the experiment forthwith

14. This does not preclude any treatment or procedure done o the organ or tissue after removal from the donor's body aimed at reducing its antigenicity and improving graf survival.

Guidelines on Cadaver donor transplants

1. Every one of us should give a thought to the need for orga donation after death.In such an event one should make decision and inform the next of kin, and register onesel with an appropriately constituted authority. Where one i opposed to donating his or her organs, this too, should b made known to the next of kin, so that this wish of th deceased may be respected after death. Such a "Living Will is in vogue in a number of countries in the world.

2. In the absence of such prior directions from the deceased the person in lawful possession of the body will make th decision to use the organs or not, as he may think fit after consultation with the family.

3. It is important that the medical team use the body only fo the purpose to which the deceased had consented before death, or to which the family had acceded afterwards.

4. Remaining tissue and organs should be treated with the respect due to a human body, and will not be used for any purpose to which explicit consent had not been given.

5. Under no circumstances should financial gain be made from any such procedure.

6. There shall be no coercion and no monetary inducements offered to the family of the prospective cadaver donor.

7. Confidentiality of the donation must be maintained from both sides: the recipient and his or her family will not be informed of the identity of the donor, and the family of the

donor will equally be kept unaware of who receives the donated organ. This is essential to avoid any form of exploitation by the donor's family.

Guidelines on recipients of transplants

1. The patient with failure of a vital organ is at a particular disadvantage in developing countries due to the enormous cost involved for the available interventions. If the organs involved are the kidneys, most Indians cannot afford to maintain themselves on dialysis. Similarly ventilators are available at very few centres. There are no artificial supports for other organs like the heart, the lungs and the liver, so death is imminent and no means is available to keep the individual alive short of replacing the organ concerned. Thus a measure of urgency is introduced into the search for a donor organ.

2. A desperate patient may consent to procedures which put him or her at risk. It is all the more important that every research protocol for transplantation should be carefully reviewed by a committee of suitably **qualified scientists, jurists and other eminent members of society,** so that its scientific and ethical basis may be impartially evaluated.

3. The transplant research team should have high technical expertise.

4. Adequate data management, tissue storage, and surveillance procedures should be available in a centre before it is authorised to conduct research into transplantation.

5. If, at any time, a patient should refuse to take part as a subject for a research project, it should in no way interfere with his or her right to receive treatment of the best quality which the team is capable of providing.

6. Under no circumstances should there be a conflict between scientific content of a study and the best interests of the patient. Should there be need to choose, the experiment should be abandoned and the patient should receive the best treatment possible.

Recommended reading

1. Kjellstrand CM, Dosseter JB, (eds): Ethical Problems in Dialysis and Transplantation, p 163-168. Dordrecht, Kluwer Academic Publishers, 1992.

2. The Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol 2, pp 181-182. Washington DC, US Government Printing Office, 1949. World Medical Association, Declaration of Helsinki. Latest amendment. 41st World Medical Assembly, Hong Kong, 1989.

IV. EMBRYONIC AND FOETAL TISSUE AND ORGAN TRANSPLANTATION

INTRODUCTION

Human foetal tissue has been used in research for a wi
range of purposes over decades. The thought of using foetal cel
as transplants was first occasioned when scientists attempted
find ways of treating patients with loss of nerve cells in t
brain and spinal cord. Since damaged nerve cells do n
regenerate, repair to damage in the brain and spinal cord
severely limited. Attempts to trick the neurones into repair a
re-growth have yet to bear fruit. That was when the attempts
transplant healthy neural tissue into damaged areas of the bra
in an effort at allowing the re-establishment of damaged neur
circuits were started. The immunological complication th
results whenever any foreign tissue is transplanted into a hum
was a barrier.

The use of foetal tissue is one of the means to minimise t
chances of rejection. In the early weeks after conception, foet
cells multiply rapidly and show very little antigenicity becaus
it has not yet developed many surface antigens. These cells a
not fully differentiated and adapt easily to the signals receiv
from surrounding tissue in a host. They grow and differentiate
such a manner that they are integrated to form part of the hos
organ. Foetal cells can also be successfully preserved by cooli
and reanimated. As the technology for developing immortal foeta
cell lines for study of gene regulation, pattern formation
embryogenesis, models of cell interaction and function, vaccin
development, cell growth and regulation, cancer, and the immun
response was perfected, hopes for the use of these cells a
transplants strengthened.

Non-neural foetal tissue transplantation has include
injection of immune cells from the thymus and liver of aborte
foetuses into the umbilicus of a 30-week-old foetus with bar
lymphocyte syndrome, a rare and always fatal immunodeficienc
disorder. Success has also been reported in the use of foeta
thymus in the reconstitution of a severe combine
immuno-deficient (SCID) child in Italy. The child is now 17 year
old and exhibits normal immune responses even though his T cell
are of foetal donor origin. Other potential uses of foeta
tissue include treatment of diabetes, genetic retina
abnormalities, optic nerve and spinal cord injury, Alzheimer'
disease, aplastic anaemia, acute leukaemia/lymphoma and live
failure.

DEFINITIONS

Embryonic state: between 15 days and 8 weeks post-conception of
pregnancy. In the absence of more precise information (i.e
menstrual cycle length), conception is presumed to have taken
place two weeks after the beginning of the woman's last
menstrual period. The distinction of the 15-day stage as the

beginning of the embryonic stage is not arbitrary: the pre-embryo is not isomorphic with the later developmental stages, since cells cannot yet be defined as contributing to the embryo or to the extra-embryonic tissue, and complete implantation has not yet been accomplished. At 8 weeks the rudiments of nearly all the main structures have been laid down and there is a general appearance of a mammal-to-be with four limbs and a head.

Foetal stage: Subsequent period between 8 weeks and the time the baby is born, at approximately 38 weeks post-conception (40 weeks post-last menstrual period). Live aborted foetus: 'If an aborted foetus is alive, it is a person, no matter how short the period of gestation, and using it for an experiment would, in law, be at least an assault upon it. If doctors wish to perform experiments legally, they must seek statutory authority.' (Keown 1993)

Dead fetus: An expelled or delivered foetus that exhibits no heart beat or spontaneous breathing. Some organs, tissue and cells remain alive for varying periods after the moment of death of the foetus.

Neonate: Newly born, live individual of any gestation period.

Suggested Guidelines on research using foetal tissue or organs for transplantation in India

1. Every transplantation or research project involving the use of embryonic or foetal tissue must be approved by the local scientific and ethics committees.

2. All members of the hospital or research staff - medical and paramedical - directly involved in any of the procedures will be fully informed of the purpose and implications of the research project.

3. The researcher shall not be a party to deliberate conception and/or subsequent abortion for the sake of obtaining tissue or organ for research or saving the life of a family member or for the purpose of commercialisation.

4. Tissue for transplantation or research may be obtained from dead embryos or foetuses, their death resulting from legally induced or spontaneous abortion. Death of an intact embryo or foetus is defined as absence of respiration and heart beat.

5. Voluntary, informed, written consent will be obtained from the mother in two stages - first for the abortion; next for the donation of tissue from the foetus. The mother's decision to donate foetal tissue is sufficient for the use of the tissue unless the father objects in writing. In cases of incest or rape, the father's objection carries no significance.

6. The mother will not dictate who shall receive the foetal tissue taken for transplantation.

7. Anonymity of donor and recipient will be maintained so that neither party is aware of the identity of the other.

8. The procedure of abortion, or its timing, will not be influenced by the requirements of the transplantation activity. These should be based solely on concern for the safety of the mother.

9. Those participating in termination of pregnancy will not, in any way, be party to the subsequent usage of embryonic or foetal tissue or profit from such usage.

10. The procurement of embryos, foetuses or their tissue will not involve profit or remuneration.

11. Intact embryos or foetuses will not be kept alive artificially for the purpose of removing usable material.

12. Tissues from aborted foetus can be cultured and banked for use in research on transplantation. If such stored tissue is to be subsequently used for any purpose other than the original objective,a fresh sanction will be obtained from the scientific and ethical committees.

13. Cells obtained from foetuses will not be patented with a view to making profits from their subsequent usage.

14. Use of umbilical cord blood from a live foetus or neonate for transplantation: The fundamental principle in any operation on a live foetus or neonate will be to ensure that no harm will follow to the foetus or neonate. Since the exact timing of the clamping of the umbilical cord has a significant impact on the neonate and early clamping may cause an abrupt surge in arterial pressure resulting in cerebral intra-ventricular haemorrhage, particularly in premature neonates, normal clamping protocol will be followed when collecting foetal blood for transplantation. There is a risk that the neonate donor will develop a need for his or her own cord blood later in life. If the blood has been used for another, he or she might be without blood when it is needed. Parents will be fully informed of the risks of the donation and written consent obtained from them on behalf of the foetus.

15. Use of tissue or organs from dead anencephalic foetus or neonate (foetus or neonate lacking brain development above the level of the brainstem) is permitted. Physicians may provide anencephalic neonates with ventilator assistance and other medical therapies that are necessary to sustain organs till such time as the diagnosis of death is made on the basis of cessation of cardiac function. Retrieval and transplantation of organs of anencephalic fetus are

ethically permissible only after such diagnosis of death is made.

16. Whilst the transplantation of tissue from one animal into another is permissible when a rational explanation for such experimentation has been provided, transplantation of foetal tissue into man is subject to much greater scrutiny.

17. No transplantation of foetal tissue into man will be permitted unless the following criteria have been met:

    i. There will be a detailed scientific basis for such transplantation.

    ii. Animal experiments must have shown successful results - eradication of disease, elimination or amelioration of symptoms and signs or successful substitution of deficient chemicals and restoration of normal physiological function by the transplant. These must be documented in one or more indexed journals with good peer review mechanisms.

    iii. All records pertaining to animal experiments must be complete and submitted to specialist and general scientific scrutiny. These records must be preserved for a minimum period of five years after the completion of the study preferably on a permanent basis as far as possible.

    iv. Success in animal experimentation must be shown on a long-term basis. The studies must include investigations on animals receiving the transplants at periodic intervals after the proceduret specially with reference to unequivocal demonstration of absence of any transmission of disease through the transplant.

    v. Trials in human patients will commence only on those patients where no other form of treatment is available and where, in the absence of the transplant, the patient is likely to suffer relentless deterioration in his health with fatal termination.

    vi. After obtaining her consent, the mother must be screened for transmissible disease. If possible, the material to be transplanted must also be similarly screened.

    vii. Trials in human patients will be carried out only at the institutions having clinical and research facilities needed for such trials, including those that may be required to treat complications that may follow such research.

    viii. The research group and the institution/s in which they work will undertake to conduct at free cost the

research on their human subjects and also trea
completely any complication that may follow their stud
even if it appears several years after the conclusio
of the study.

ix. The research group will provide the human subjects
printed document explaining in simple, non-technica
language, the purpose of the study, details of th
procedures the human subject is to undergo
complications that may follow these procedures
financial implications, interests of the researchers i
the conduct of the study, and a commitment to trea
completely and free of cost any complication that ma
ensue. The human subject must certify in writing tha
he has studied and understood the contents of thi
document and that he/she is willing to participate i
the study.

x. Any adverse effects noted will be immediately discusse
with members of the ethics committee and the projec
grounded if these cannot be explained or reasonabl
corrected in the course of the study.

18. The local ethics committee must ensure report-back measure
at every stage of research and confirm that a detaile
report on the procedures, findings and conclusions i
submitted to an indexed journal for publication even whe
the results are of a negative nature.

19. As with therapeutic transplantation, constantly update
local (metropolitan), regional or national lists o
available tissues and organs should be set up to ensure that
optimal use is made of all available donations. These lists
should be made freely available to all authorised research
workers.

Recommended reading

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Current opinions with annotations 1996- 1997 Edition,
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or foetal tissue for experimental and clinical
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8. OPRR NIH: Protecting human research subjects. Institutional Review Board Guidebook. United States Department of Health and Human Services. 1993.

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V. *XENO-TRANSPLANTATION*

INTRODUCTION

Paucity of organs from humans for transplantation into other humans has led to the search for other sources such as animals. Initially the focus was on the great apes as they appear to be nearest to man in the evolutionary scale. It was soon realised that unbridled use of simians would lead to possible extinction of their species. Attention has thus turned to other animals.

DEFINITIONS

Primates: The most highly evolved of animals. Includes simians and homo sapiens.

Simians: The monkey species, including the great apes.

Species: Group of individuals sharing similar biological characteristics and who can breed within the group to produce fertile offspring.

Source animal: Animal from whom tissues or organs are removed for transplantation in humans. The term 'donor animal' has been discarded as the animals are not permitted any choice.

Tissue: A collection of similar cells, all of which perform the same function. An example is neural tissue within the brain.

Transgenesis: The introduction of a foreign gene into an anima
or organism. The transferred gene is called transgene.

Xeno-transplant: Transplant of tissue or organ from one species
to another. Here, we are principally concerned with transplants
from animal to man.

Zoonoses: Diseases peculiar to animals in the normal course of
events that can, under special circumstances - as after
xeno-transplant - be transferred to man.

Animals that can be used as sources of tissue or organ for man

Our immune responses are likely to reject all foreign tissue
and organs transplanted into us. The chances of rejection are
minimised if the source animal is genetically similar to man.
This is the reason for considering the great apes as likely
sources.

Once the apes were ruled out, in order to preserve their
species, attention turned to cattle, sheep and pigs. In each of
these species, transplant of unaltered tissue or organ will
certainly lead to rejection.

Pigs are currently the animals of choice as the size of
their organs and the anatomical and physiological loads they must
carry are similar to those in man. Besides, pigs breed easily and
are maintained without much difficulty. Experimental studies have
been carried out on kidneys, liver, heart, heart valves and bone
marrow, islet cells of the pancreas and nerve cells obtained from
pigs with encouraging results.

Attempts are on so that pigs be engineered to possess
genetic material similar to that in man. This is done by
replacing porcine genes by human genes into the cell that will
form the pig embryo. Tissues and organs from such transgenic
pigs will, it is hoped, stand the scrutiny by the immune systems
of the patients into whom they are transplanted and will be left
unmolested. However, there are possible problems in using
porcine tissue or organs in human transplantation. The average
pig survives for only twenty years. Will transplanted tissues
function efficiently in man with a life span of three score years
and ten, or will they fail after two decades, necessitating
further transplants?

Equally worrying is the possibility of transferring germs
and viruses peculiar to pigs into man through transplanted
tissues. We are aware of species-specific infective diseases that
limit themselves to that species. Under special circumstances -
as after transplantation - such organisms may make the leap from
one species to another and cause untold havoc in the new species
which has no immunity against them. Some of the most deadly
viruses currently devastating individuals and groups in some
African countries - that causing Lassa Fever, the Marburg virus
and the Ebola virus are such examples. They appear to have spread

from bats or other animals to man. The human immunodeficiency virus (HIV) also appears to fall into this category. These questions are still unresolved.

Apart from the known bacteria, fungi and viruses, there is concern for those hitherto unknown and undetected, especially so with **slow viruses**, that produce manifestation of the disease years - often decades - after they gain entry into our systems.

Equally disquieting is the fact that once an infective organism makes a jump across species, it may spread like wildfire in the new species - in this case, man.

Ethical considerations

Transmission of disease from animal to man:

There has been considerable apprehension that tissues or organs transplanted from animal to man may convey infection or unwanted genetic abnormalities. This anxiety has prompted most countries, to ban all research on transplanting animal organs to human beings till this issue has been satisfactorily addressed. Measures proposed include the breeding of successive generations of animals and studying them for all known and possible unknown organisms that can cause disease. Only those animals certified free from disease could be considered for transplantation.

It is also proposed that extensive research, with long-term follow-up studies be carried out on animal-animal transplants so that we may learn of possible pitfalls and develop measures to avoid them before undertaking the first experiment involving man.

Guidelines on xeno-transplantation

1. Experimental xeno-transplantation must only be permitted between different animal species. **Animal - to - man transplants must not be permitted at the present level of knowledge.**

2. Institutional scientific and ethics committees must approve of such research studies, with special attention being paid to their relevance, availability of facilities for extensive, sophisticated and long-term studies for transmission of disease through transplantation.

3. An advisory committee consisting of reputed scientists in the field, medical professionals, veterinary experts and microbiologists must oversee all such transplants.

4. Records on all research studies must be detailed, scrupulously maintained and kept available for a long period of time - perhaps decades.

5. Safeguarding the interest of the pioneer human recipients when such transplants are permitted in future.It is proposed

that each and every animal - to - man transplant be ver
carefully vetted and sanctioned on a case-by-case basis. I
each instance, extensive studies on the animals to ensur
freedom from infection must be made mandatory. The huma
recipients of tissues or organs must be carefully followe
up over a long term.

Recommended reading

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2. Anonymous: Guidelines for the care and usage of animals in scientific research. New Delhi: Indian National Science Academy. 1992.

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6. Coats ME: The germ free animals in research. New York: Academic Press. 1968.

VI. TRANSPLANTATION FOR COSMETIC PURPOSES

1. Research on transplantation for cosmetic purposes (such as the creation of a new ear after transferring tissue from the patient on to a mould which is later implanted into the subcutaneous tissue of a transgenic mouse) will be governed by the same principles as those in using donation of tissue or organ from a live donor.

2. Donation of tissue should be restricted to renewable tissues like skin to an extent where such removal will not greatly alter the normal functions of such tissue.

3. It is imperative that no risk be imposed whilst removing tissue beyond that inherent in surgery. Any manner of experimentation,though it may be intended to improve the survival of the graft, should be prohibited if there is the slightest extra risk to the donor. Examples are pre-treatment of the donor with immunosuppressives or anticoagulants.

4. Every such research project should be preceded by careful assessment of predictable risks in comparison with

foreseeable benefits and improvement in the success rate of transplantation.

5. The patient must be informed of all possible risks, including those of failure of the transplant in a manner easily understood by him, before his consent is taken.

6. It follows that the donor should have the legal capacity to give consent; should be in a position to exercise free power of choice,without the slightest element of force, duress, or coercion; and should have sufficient knowledge and comprehension of the subject to be able to make a decision with full understanding of the consequences. Children and mentally incompetent adults so also persons with limited autonomy should not be subjected to such surgery.

7. The experiment should be such as to yield fruitful results for the good of patients who need transplantation without having the donor. The experiment should be undertaken only if there is no other method available of finding the answer to the question raised.

8. The experiment should be so planned and conducted as to avoid all unnecessary risks to the donor, to the tissue to be transplanted, and to the recipient site.

9. Where tissue is to be temporarily transferred to an animal, all necessary precautions should be taken, and adequate facilities should be available, to protect the patient from the most remote possibility of harm.

10. The subjects should be at liberty to withdraw from the experiment and to abrogate the consent earlier given, with no requirement to offer any explanation of the reasons for his or her doing so.

STATEMENT OF SPECIFIC PRINCIPLES FOR CLINICAL EVALUATION OF DRUGS /DIAGNOSTICS/VACCINES/HERBALREMEDIES *ETC.*

Human studies designed to evaluate the safety, effectiveness, or usefulness of an intervention include research on therapeutics, diagnostic procedures and preventive measures including vaccines. The type of experimental procedures that a patient is submitted to has become more complex and varied as the complexities of medical research have increased. It is clearly accepted that it is essential to carry out research on human subjects to discover better medical and therapeutic modalities for the benefit of mankind. It is equally clear that such research on normal subjects and patients is associated with some degree of risk to the individual concerned. The guidelines have been framed to carry out the evaluation of drugs, vaccines, devices and other diagnostic materials on human subjects including herbal remedies, in accordance with basic ethical principles. These guidelines are important for the protection of research subjects against any avoidable risk and to guide the researchers in the preparation of research proposals/protocols.

For the evaluation of proposed research intervention the framework of guidelines is as follows:

A. General Ethical Principles

B. Special Ethical concerns related to

1. Drug Trials
2. Vaccine Trials
3. Medical Devices
4. Diagnostic agents - with special reference to use of Radioactive Materials and X-rays
5. Trials with Herbal remedies.

A. GENERAL ETHICAL PRINCIPLES

All the research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for person/subject, beneficience and justice. The guidelines laid down are directed at application of these basic principles to research involving human subjects.

An investigator is the person responsible for the clinical trial and for the rights, health and welfare of the subjects recruited for the study. He/she should have qualification and competence in clinical trial research methods for proper conduct of the trial and should be aware of and comply with the legal and ethical requirements of the study protocol.

1. *Informed Consent of Subject*

1.1 Individual Informed Consent

For all biomedical research involving human subjects, th investigator must obtain the informed consent of the prospectiv subject or, in the case of an individual who is not capable o giving informed consent, the consent of a legal guardian.

- Informed consent is based on the principle that competen individuals are entitled to choose freely whether t participate in research or not. Informed consent protect the individual's freedom of choice and respect fo individual's autonomy.

- When research design involves no more than minimal risk (fo example, where the research involves only collecting dat from subject's records) the ethical review committee ma waive some or all elements of informed consent.

1.2 Essential information for prospective research subjects

Before taking the informed consent of subject, th investigator must provide the individual with the followin information in the language he or she is able to understand -

- the aims and methods of the research,
- the expected duration of the subject participation,
- the benefits that might reasonably be expected as an outcom of research to the subject or to others,
- any risk to the subject, associated with study,
- maintenence of confidentiality of records,
- responsibility of investigators,
- provision of free treatment for research related injury,
- compensation of subjects for disability or death resultin from such injury, and
- freedom of individual to participate and to withdraw fro research any time without penalty or loss of benefits t which the subject would otherwise be entitled.

1.3 Obligations of investigators regarding informed consent

The investigator has duty to:

- communicate with prospective subject all the information necessary for informed consent. There should not be an

restriction on subject's right to ask any questions related to study, and any restriction on this undermines the validity of informed consent.

- exclude the possibility of unjustified deception, undue influence and intimidation. Deception of the subject is not permissible. However, sometimes information can be withheld till the completion of study, if such information would jeopardize the validity of research.

- seek consent only after prospective subject is adequately informed. Investigator should not give any unjustifiable assurances to prospective subject, which may influence the subject's decision to participate in the study.

- as a general rule obtain from each prospective subject a signed form as an evidence of informed consent (written informed consent) preferably witnessed by a person not related with trial, and in case of incompetence, a legal guardian or other duly authorised representative should do so.

- renew the informed consent of each subject if there are material changes in the conditions or procedures of the research along the trial.

- Intimidation in any form invalidates informed consent. The investigator must assure prospective subjects that their decision to participate or not will not affect the patient - clinician relationship or any other benefits to which they are entitled.

1.4 Inducement to participate

Subjects may be paid for the inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research. They may also receive free medical services. However, payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in research against their better judgement (inducement). All payments, reimbursement and medical services to be provided to research subjects should be approved by the Ethical Committee.

- When a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses.

- When a subject is withdrawn from research for medical reasons related to the study the subject should get the benefit for full participation. When a subject withdraws for any other reasons, he/she should be paid in proportion to the amount of participation.

2. *Selection of Research Subjects*

2.1 Equitable distribution of burdens and benefits

Effort may be made that individuals or communities invited for research should be selected in such a way that the burdens and benefits of the research should be equally distributed. Special justification is required for inviting vulnerable subjects, whose rights and welfare must be protected.

Vulnerable subjects:- Equitable distribution of the burdens and benefits of research participation is generally more difficult when the intended subjects include vulnerable individuals or groups. These subjects are children, persons with mental or behavioural disorders, who are incapable of giving informed consent and prisoners, students, subordinates, service personnel etc. who have reduced autonomy. Adequate justification of their involvement as research subjects is required.

The quality of the consent of certain social groups requires careful consideration, as their agreement to volunteer may be unduly influenced by the Investigator.

2.2 Selection of pregnant or nursing women as research subjects:-

As a general rule, pregnant and nursing (breast feeding) women should not be subjects of any clinical trials except such trials which are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants, and for which drugs can be tested only in pregnant women.

The justification of participation of these women in clinical trials would be that they should not be deprived arbitrarily of the opportunity to benefit from investigations, drugs, vaccines or other agents that promise therapeutic or preventive benefits. Example of such trials are, to test the efficacy and safety of a drug for reducing perinatal transmission of HIV infection from mother to child, trials for detecting fetal abnormalities, trials of therapies for conditions associated with or aggravated by pregnancy etc.

Women should not be encouraged to discontinue nursing for the sake of participation in research and in case she decides to do so, harm of cessation of breast feeding to the nursing child should be properly assessed.

Research related to termination of pregnancy:- Pregnant women who desire to undergo Medical Termination of Pregnancy (MTP) could be made subjects for research relating to termination of pregnancy, as per The Medical Termination of Pregnancy Act, 1971.

Research related to pre-natal diagnostic techniques:- In pregnant women research on prenatal diagnostic techniques should be limited to detect the fetal abnormalities. Such research

should take the consideration of The Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994.

2.3 Research involving children

Before undertaking children as subjects for clinical trial, the investigator must ensure that -

- children will not be involved in research that might be carried out equally well with adults,

- the purpose of the research is to obtain knowledge relevant to health needs of children. For a new drug usually the study in children should always be after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in a primary disease of the children,

- a parent or legal guardian of each child has given proxy consent on behalf of the child,

- the consent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors, adolescents *etc.*,

- research involving children should be conducted in settings in which the child and parent can obtain adequate medical and psychological support,

- interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child subject must be justified in relation to anticipated risks involved in the study. The risks of interventions that are not intended to be of direct benefit to the child subject must be justified in relation to anticipated benefits to society.

3. *Confidentiality of Data*

3.1 Safeguarding confidentiality

The investigator should safeguard the confidentiality of research data, which might lead to the identification of individual subjects.

Data of individual subjects can be disclosed only in a court of law under the orders of the presiding judge or in some cases may be required to communicate to drug registration authority or industrial sponsor of research or in cases of certain communicable diseases to health authority. Therefore, the limitations in maintaining the confidentiality of data should be anticipated and assessed.

4. *Compensation of Research Subjects from Accidental Injury*

4.1 Right of subjects to compensation

Research subjects who suffer physical injury as a result o their participation are entitled to financial or other assistanc to compensate them equitably for any temporary or permanen impairment or disability. In case of death, their dependents ar entitled to material compensation.

Obligation of the sponsor to pay:- The sponsor whether pharmaceutical company, a government, or an institution, shoul agree, before the research begins, to provide compensation fo any physical injury for which subjects are entitled t compensation.

5. *Ethical Review Committee*

All trials involving human subjects must be submitted fo scientific review and approval of ethical review committee o institute before starting such research.

All the medical colleges and research institutions/centre involved in clinical research should form scientific and ethica committees which may be either combined or be two independen committees. The scientific evaluation will assess the technica excellence of the proposed clinical trial.

5.1 Composition of the Ethical Committee

The ethical committee should be able to provide complete an adequate review of the research proposals submitted to them. Th committee should be headed by a chairman, who should not be hea of the same institution. Other members should be – on pharmacologist preferably clinical pharmacologist if available one pathologist, two clinicans, one or more members o non-clinical departments, one person having knolwedge of la (preferably a Judge or Lawyer) and a social scientist o philosopher. The member secretary should be from the Institut concerned.

The number of persons in an ethical committee be kept fairl small (5-7 members). The ethical committee at any institutio should not hesitate to have as its members, individuals fro other institutions or communities if required. If th Investigator is a member of the Institutional Ethical Committee he/she should not be present when his/her own project i discussed.

5.2 Basic responsibilities

The ethical committee should meet periodically (at leas twice a year) and review all research proposals and thei progress reports. **Ethical approval through circulation o research proposal among members should not be resorted to.** Th basic responsibilities of ethical committee are -

- to verify the safety, integrity and human rights of the subjects participating in the trials.

- to verify that all proposed interventions, and particularly the administration of drugs and vaccines or use of medical devices under development, have been assessed by a competent expert body as acceptably safe to be undertaken in human subjects; and

- to ensure that all other ethical and scientific concerns arising from a protocol are satisfactorily resolved both in principle and in practice.

5.3 Assessment of research proposal

The ethical committee should review every research proposal on human subjects. It should observe that the research proposal is scientifically sound, the possible risks to the subjects are justified by the expected benefits, informed consent is satisfactory and procedures for selection of subjects are equitable and properly documented.

The protocol should include -

- clear research objectives and rationale for undertaking the investigation in human subjects in light of the existing knowledge,

- precise description of methodology of the proposed research, including intended dosages of drugs and planned duration of treatment,

- a description of plans to withdraw or withhold standard therapies in the course of research,

- the plans for statistical analysis of the study,

- inclusion and exlusion criteria for admission of subjects in the study,

- prccedure for seeking and obtaining informed consent,

- safety of proposed intervention and any drug or vaccine to be tested, including results of relevant laboratory and animal research, and

- for research carrying more than minimal risk, if any, an account of plans to provide medical therapy for such risk or injury should be included.

- storage and maintenance of all data collected during the trial.

The role of ethical committee is not only to permit the

initiation of research but also to review research during the course of study. When there is anticipation of likely injury or detection of adverse events during the course of study the termination of study should be recommended.

6. *Externally Sponsored Research*

The externally sponsored research entails two ethical obligations:-

- The external sponsoring agency should submit the research proposal according to the standards applied by ethical committee of sponsoring agency/country with due approval.

- The ethical committee of host Institution/country should satisfy themselves that the proposed research meets their own ethical requirement before sanctioning approval. The decision of the host Institution where the study will be conducted is ultimate.

B. ETHICAL CONSIDERATIONS FOR SPECIFIC AREAS

I. DRUG TRIALS

Clinical trial of drugs is a controlled study in human subjects, designed to evaluate propsectively the safety and effectiveness of new drugs/new formulations.

The proposed trial should be carried out, only after approval of the Drugs Controller General of India, as is necessary under The Schedule Y of Drugs and Cosmetic Act, 1940. The investigator should also get the approval of Ethical Committee of the Institution before submitting the proposal to DCI. The guiding principles should be followed irrespective of whether the drug has been developed in this country or abroad or whether clinical trials have been carried out outside India.

1. Phases of clinical trials

The following four phases of clinical trials of drug require ethical clearance -

1.1 Phase 1 drug trials:- The objective of phase 1 of clinical trial is to determine the maximum tolerated dose in healthy adult male. To establish the safe dose range, pharmacokinetic, pharmacodynamic effects, and adverse reactions, if any, with their intensity and nature. These studies should be carried out by investigator trained in clinical pharmacology.

1.2 Phase 2 drug trials:- These are controlled studies conducted in a limited number of patients to determine therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics.

1.3 Phase 3 drug trials:- The purpose of these trials is to obtain sufficient evidence about the efficacy and safety of drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. On successful completion of phase 3 trials the permission is granted for marketing of drug.

1.4 Phase 4 drug trials:- After approval of drug for marketing, phase 4 trial or post marketing surveillance is done to delineate additional information about the drug's risks, benefits and optimal use. Although, this is outside the purview of ethical committee, it is an important aspect of drug trial on the long term effects of the drugs.

Throughout the drug trials, the distinction between therapy and research must be maintained. A physician/investigator who participates in research by administering the new drug to consenting patients must ensure that the patients understand and remember that the drug is experimental and that its benefits for the condition under study are unproven. Use of Placebo in drug trials has come under severe scrutiny at the present age and requires careful consideration before approval. Trials of drugs without approval of appropriate authority should be dealt according to law of the land and regulatory agencies.

Model protocols recommended by WHO Guidelines for Good Clinical Practices (GCP) for trials on pharmaceutical products and Drugs Controller General of India's Guidelines for Good Clinical Trial Regulations are included at the end of the text.

2. Special concerns for Multicentric Trials

A multicentric trial is conducted simultaneously by several investigators at different centres following the same protocol and proformae. Ideally, these trials should be initiated at the same time at all the centres.

- All the Investigators should give a written acceptance of the protocol to be followed for the trial duly approved by the ethics committee of the host institutes.
- Meetings to be organised at the initial and intermediary stages of the trial to follow uniform procedures at all centres.
- Training to be imparted to participating centres to familiarise with the uniform procedure.
- Standardisation of methods for recruitment, evaluation and laboratory procedures.
- Control of adherence to protocol including measures to terminate the participation of some centres, if necessary.
- Specific role of coordinators and monitors.

- Centralised data management and analysis.

- Drafting of a common final report and publication procedur

2.1 Monitoring and reporting Adverse Events

Any serious adverse events occurring during the course the trial should be immediately brought to the attention ethics committee, sponsors and Drug Controller of India. At t end of the trial, all adverse events are to be listed, evaluat and discussed in detail in the final report.

II. CLINICAL EVALUATION OF VACCINES

The guidelines to conduct the clinical trial investigational vaccines are similar to those governing a dr trial.

1. Phases of vaccine trial

1.1 Phase I trial refers to the first introduction of a vacci into a human population for determination of its safety a biological effects including immunogenicity. This phase include study of dose and route of administration and involves less tha 100 volunteers. Phase I trial should involve low risk subjects For example, immunogenicity to hepatitis B vaccine should not b determined in high risk subjects.

1.2 Phase II trial refers to the initial trials examinin effectiveness (immunogenicity) in a limited number (200-500) o volunteers. It may be ethically justified to involv HIV-seropositive individuals as subjects in phase II trial fo HIV vaccines.

1.3 Phase III trials focus on assessment of safety an effectiveness in the prevention of disease, involving controlle study on a larger number of volunteers in multicentres.

2. Points to be noted in vaccine trials

2.1 Some vaccines that contain active or live - attenuate micro-organisms have a small risk of producing tha particular infection. Subject to be informed of the same.

2.2 The subjects in control groups or in case of ineffective vaccines, are at risk of contracting the disease.

2.3 The risks associated with vaccines produced by recombinant DNA techniques are yet unknown.

2.4 Trials should be designed to involve subjects who stand to benefit most from the protection afforded by the vaccine.

2.5 Exact information about what to do and whom to contact in case of a serious adverse reaction or research related injury, should be given to the participants.

III. CLINICAL TRIALS WITH MEDICAL DEVICES

The concept of regulations governing investigations involving medical devices is relatively new. Recently it has been realised that the risk involved in the use of such devices should be identified before they are put to public use.

DEFINITIONS

Medical devices

A medical device is defined as an inert diagnostic or therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body unlike the medicated devices which contain pharmacologically active substances which are treated as drugs. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, orthopedic pins and other orthopedic accessories.

Depending upon risks involved these devices could be classified as follows -

a) **Non significant risk devices** - An investigational device that does not present significant risk to the patients

b) **Significant risk devices** - An investigational medical device that presents a potential serious risk to the health, safety or welfare of the subject - for example, heart valve.

All the general principles of clinical trials described for drug trials should also be considered for trials of medical devices. However, the following important factors which are unique to medical devices should be taken into consideration while evaluating the related research project.

1. Medical device should have been cleared for trial by Drugs Controller of India.

2. Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.

3. Clinical trial of medical devices are different from drug trials, as former cannot be done in healthy volunteers. Hence Phase I of Drug Trials is not necessary for Device trial.

4. Medical devices used within the body may have greater risk potential than those used on the body - for example, orthopedic pins vs crutches.

5. Medical devices not used regularly have less risk potenti
than those used regularly. For example: Intraocular lens
contact lenses.

6. Safety of the procedure to introduce a medical device in t
patient should be considered, as the procedure itself m
cause harm to the patient.

IV. DIAGNOSTIC AGENTS - USE OF RADIOACTIVE MATERIALS AND X-RAY

In human beings, for investigation and treatment, differe
radiations - X-ray, gamma rays and beta rays, radiopaque contra
agents and radioactive materials are used. The relative ris
and benefits of research proposal utilising radioactive materia
or X-rays should be evaluated. Radiation limits for the use
such materials and X-rays should be in accordance with the limi
set forth by the regulatory authority (BARC) for such material

Points for consideration:

- can the information to be gained be gathered using metho
that do not expose subjects to more radiation than expos
normally,

- the research be performed on patients undergoing th
procedures for diagnostic or therapeutic purposes,

- safety measures to be taken to protect research subjects a
others who may be exposed to radiation,

- the protocol should make adequate provisions for detecti
pregnancies to avoid risks of exposure to embryo,

- information to subject about possible, if any genetic damag
to offspring,

- non-radioactive diagnostic agents are considered as drug
and same guidelines should be followed when using them.

V. CLINICAL EVALUATION OF HERBAL REMEDIES AND MEDICINAL PLANTS

The guidelines given below relate to herbal remedies an
medicinal plants which are to be clinically evaluated for use i
the allopathic system of medicine and which will be used i
allopathic hospitals. The evaluation also will be carried out i
allopathic hospitals and the registration of the plant extract o
compound will follow the procedure laid down by the office of th
Drugs Controller General of India for allopathic drugs. Thi
does not pertain to guidelines for ayurvedic drugs or unani drug
to be clinically evaluated by experts in those systems o
medicine to be eventually used by ayurvedic and unani physician
in their own hospitals and clinics.

All the general principles of clinical trials described earlier pertain also to herbal remedies. However, there are special features regarding herbal remedies which need to be kept in mind during their clinical evaluation.

The first feature is that at the time of clinical evaluation a lot may be known about the plant or its extract. There could be extensive literature about use of this in ancient Ayurvedic or Unani literature and other organised systems or, indeed, the plant may actually be in use by physicians of the traditional systems of medicine for a number of years. The substance to be clinically evaluated will be used as is being used now or as has been described in the texts.

The second consideration is that it is possible that clinical evaluation of a plant extract or a compound isolated from an extract has to be carried out which has never been in use before and has not ever been mentioned in ancient literature.

The guidelines for these two types of substances cannot be the same and therefore, given below are specific guidelines for substances which could fall into either group.

A. For plants and herbal remedies currently in use or mentioned in literature of any organised system of medicine

It is important that the herbal preparation to be clinically evaluated has been described in an authentic and recognised text of the particular system of medicine and prepared strictly in the same way, incorporating GMP norms or standardisation as far as possible. It may not be necessary to undertake phase I studies. No toxicity study may be needed for phase II trial unless there are reports suggesting toxicity or the use is to be for more than 3 months. It should be necessary to undertake 2-4 weeks toxicity study in 2 species of animals in the circumstances pointed out in the preceding sentence or when a larger multicentric phase III trial is subsequently planned based on results of phase II study.

Clinical trials with herbal preparations should be carried out only after these have been standardised and markers identified to ensure that the substances being evaluated are always the same. The recommendations made earlier regarding informed consent, inducements for participation, information to be provided to the subject, withdrawal from study and research involving children or persons not in full control of their senses all apply to these trials. These trials have also got to be approved by the appropriate scientific and ethical committees of the concerned Institutes.

There is one special aspect which needs to be emphasised. Since the substance to be tested is already in use in the Ayurvedic or Unani System of medicine or has been mentioned in these texts, toxicity testing in animals has been considerably reduced. However, it is essential that such clinical trials are carried out only when a competent ayurvedic or unani physician is

co-investigator in this clinical trial and the clinical evaluation is carried out jointly by the allopathic physician and the specialist from the traditional system of medicine. It would not be ethically acceptable nor morally justifiable, if an allopathic physician, based on references in ayurvedic literature, carries out clinical evaluation of the plant without any concept or training in Ayurveda or the Unani System of medicine - hence the necessity for association of a specialist from these systems of medicine.

B. For new plants and extracts <u>not</u> in use or mentioned in literature

The other situation would be when an extract of a plant or a compound isolated from the plant has to be clinically evaluated for its therapeutic effect. This is, for all purposes, a new substance never been tested before. All the acute, subacute and chronic toxicity tests which need to be carried out with any new synthetic compound would need to be carried out with this preparation before clinical evaluation.

When the toxicity tests have been completed, and there is no evidence of undue toxicity a decision has to be taken whether the substance should be clinically evaluated. If the decision is made to carry out a clinical evaluation, this has to be carried out by a physician of the modern system of medicine *i.e.* allopathy. There is no need nor necessity to have a specialist in the traditional systems of medicine involved as a co-investigator in these trials as this is not an ayurvedic or unani drug and, in its present form, has not been used in the traditional systems of medicine. It should be tested just as any new synthetic drug would be tested and all the observations made earlier would also apply to this compound or extract.

Appendix 1

Model list of items to be contained in a clinical trial protocol as suggested by WHO Guidelines for General Clinical Practices (GCP)

The trial protocol should, where relevant, be required to cover the following points:-

1. Title and justification for the trial.
2. Statement of rationale, objectives and purpose of the trial.
3. Site of the trial, name and address of the sponsor.
4. Name, address and qualifications of each investigator.
5. Description of the type of trial (randomised, blinded, open), trial design (parallel groups, cross over technique), blinding technique (double blind, single blind), and randomization (method and procedure).
6. Description of trial subjects. Criteria for inclusion and exclusion of potential trial subjects and process of recruitment, types, methods and time of allocation of subjects.
7. Number of trial subjects needed to achieve the trial objective based on statistical considerations.
8. Description of and justification for route of administration, dosage, dosage interval and treatment period for the pharmaceutical product being tested and the product being used as a control. Dose-response relationships should be considered.
9. Any other treatment that may be given or permitted concomitantly.
10. Clinical and laboratory tests, pharmcokinetic analysis, *etc.* that are to be carried out.
11. Description of how responses are recorded. Description and evaluation of methods of measurement, times of measurements, follow-up procedures. Measures to control patients' compliance with the treatments.
12. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.
13. Methods of recording and reporting adverse events/reactions, provisions for dealing with complications.
14. Procedures for the maintenance of subject identification

code lists, treatment records, randomisation list and case report form (CRF). Records should permit ea identification of individual patients/participants a permit auditing and reconstruction of data.

15. Information on establishment of the trial code, where will be kept and when, and how and by whom it can be brok in the event of an emergency.

16. Measures to be implemented to ensure the safe handling ar storage of pharmaceutical products, and to promote ar control compliance with the prescibed and othe instructions.

17. Description of methodology on the evaluation of result (*e.g.* statistical methods) and on the report o patients/participants withdrawn from the trial.

18. Time schedule for completion of the trial.

19. Information to be presented to the trial subjects including how they will be informed about the trial and how and when consent will be obtained.

20. Staff instructions, *i.e.* statement of how the staff involved are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.

21. Ethical considerations and measures relating to the trial.

22. Medical care after the trial and modalities of post-trial treatment should be defined.

23. Statements regarding financing, insurance, liability, delegation/distribution of responsibilities, and publication policy, *i.e.* when serving as a contract.

24. List of literature referred to in the protocol.

Drugs Controller General of India's Guidelines for Good Clinical Trial Protocol

1. **Title:** including statement of confidentality.

2. **Unique identity code:** with date of version.

3. **Investigator(s):** name(s), degree(s), title(s), address(es), phone number(s), fax number(s).

4. **Study site:** name, address, phone number, fax number.

5. **Statement of confidentality** and bona fide disclosure.

6. **Sponsor:** name, address, phone number.

7. **Introduction:** background of and justification for the trial; appropriate references.

8. **Objectives:** questions to be answered.

9. **Design of study:** noncomparative or comparative; open, single-blind, or double blind; parallel-group or cross-over.

10. **Study subjects:** target population; sample size; criteria of diagnosis, selection and exclusion; subject information sheets; informed consent form and procedure; rules for replacement of droptouts and withdrawals.

11. **Study drugs:** dosage forms and strengths; lot numbers; packing and labelling; method of randomisation; supply, storage, dispensing and accounting; dosage regimens; method of administration; rules for breaking the code, if any; concomitant treatments allowed and not allowed.

12. **Observations to be made:** clinical and investigational; method, place, and frequency

    a) **Screening and baseline.**
    b) **Efficacy.**
    c) **Safety:** requirements of reporting non-serious and serious adverse events.
    d) **Quality of life assessment**, if any.
    f) **Healthcare economics**, if any.

13. **Data recording:** source documents; retention and archiving policy.

14. **Statistics:** sample size justification; response definitions; data to be analysed with methods and frequency of analyses.

15. **Administrative matters:** ethics committee approval; regulatory approval; risk coverage for subjects, investigator, and institution (with limitations, if any); source document verification; nature and frequency of audit for protocol compliance; policy about preparation of final report, authorship and presentation/publication; confidentiality; investigator's and sponsor's agreement.

16. **Appendices:** Case Report Form: specimen and instructions for completion; authorised signatories and their specimen signatures; Declaration of Helsinki; study flow chart; other aid memoirs for reference materials.

Note: Any amendment to any section should be approved by the ethics committee, dated, and appended to the protocol.

ETHICAL GUIDELINES FOR EPIDEMIOLOGICAL STUDIES

PREAMBLE:

Epidemiology is defined as the study of the distribution a determinants of health related states or events in specif populations and the application of this study to control hea problems. Epidemiological studies are of primary importance i large developing country like ours where the natural histor incidence, prevalence and impact on morbidity and mortality of variety of diseases are not known. It has usually been consider that epidemiology of infectious diseases is of prime importa in our country. However, the evolving pattern of change in t society with upward economic mobility and increasing number middle classes would mean that a significant number of life sty related diseases such as Ischaemic Heart Disease are increasi There is very little information about this and it would useful to undertake long term cohort studies in differe population groups.

Epidemiological studies are generally considered into t categories - **observational and experimental.** Designs of the studies are based on cross-sectional, case-control or coho approaches. Epidemiological studies cover research, progra evaluation and surveillance. Scope of ethical guidelines f epidemiological studies is concerned with epidemiologic research. Ethics in epidemiological studies is multidimensio covering clinical medicine, public health and the soci millieau.

Perhaps code of ethics is much better understood f clinical research, where the interaction between a patient and clinical researcher is of supreme importance.In epidemiologic research the researcher is dealing with group of individuals a the questions faced by an epidemiologist are more of professio nature. These questions would pertain to interactions wi individual subjects, sources of funding or employer, fell epidemiologist and the society at large. Need for code of ethi for epidemiologists is being recognised globally and the issu for such a code in the context of epidemiological research India deserve attention.

Epidemiological research differs from clinical research the context of large number of study subjects and generally long time frame. If some mistakes or aberrations get detect during the course of conduct of such studies, repeating the whc exercise will be expensive, time consuming and may not even feasible. Hence utmost care needs to be taken for vario aspects, technical, practical and ethical.

I. Observational Epidemiology:

Observational Epidemiological Research includes the following type:-

a. Cross Sectional Studies (Surveys): This is primarily population based and involves selecting stratified random samples of the population to be representative based on census data and then applying questionnaires to understand the prevalence of various diseases. Its aim is to assess aspects of the health of a population or to test hypotheses about possible cause of disease or suspected risk factors.

b. Case Control Studies: This usually compares the past history of exposure to risks among patients who have a specified condition/disease (cases) with the past history of exposure to this among persons who resemble the cases in such respects as age, sex socioeconomic status, geographic location, but who do not have the disease. (controls) Case control studies can be done by following up available records, usually records in a hospital, but in the context of a country like ours it may require direct contact between research workers and study subjects and informed consent to participation in the study is necessary. However, if it entails only a review of medical records, informed consent may not be required and indeed may not be feasible.

c. Cohort Studies: These are longitudinal or prospective studies of a group of individuals with differing exposure levels to suspected risk factors. They are observed over a long period usually several years. The rate of occurrence of the condition of interest are measured and compared in relation to identified risk factors. It requires a study of large number of subjects for a long time and involves asking questions, usually routine medical examination and sometimes laboratory investigations. Individuals are being followed up as the cohort and it is essential to identify precisely every individual to be studied. Protection of individual rights is an important issue.

II. Experimental Epidemiology:

In experimental epidemiology the investigators alter one or more parameters under controlled conditions to study the effects of the intervention. These are usually randomised controlled trials done to test a preventive or therapeutic regimen or the efficacy of a diagnostic procedure. Although these are strictly speaking epidemiological studies they come under the purview of clinical evaluation of drugs/devices/products *etc.*

SPECIAL CONSIDERATIONS FOR EPIDEMIOLOGICAL STUDIES IN INDIA

The C.I.O.M.S/W.H.O guidelines for epidemiological research assumes that the individuals or population being studied are capable of giving informed consent understanding the implications of the study. With large segments of our population, given their level of education, the full understanding in the sense of

industrialised countries may not be achievable. How the princip of "do no harm" is ensured under such circumstances without bei paternalistic is a major issue which has to be taken in consideration in ethical guidelines.

In cohort or survey techniques for incidence and prevalenc of various diseases, a major issue that has to be considered how much of intervention is justified and whether one justified in withholding interventions. For example, if you ar looking at longitudinal morbidity in a population group, shoul you give them health education which is well established wit regard to preventive aspects, or should you leave them alone s that the natural evolution of the disease can be studied? Healt education or other interventions including non-healt interventions can be quite expensive. An alternate strategy tha may be followed is to make curative therapy available to th population at their own request. This usually involves running clinic which is readily accessible to the population without an other intervention.However, it is generally considered unethica to withhold intervention or services.

General Ethical Principles:

General ethical principles of respect for persons, duty t maximise possible benefits and minimise possible harm ar important considerations in ethical guidelines. At the same tim it is essential that all individuals in an epidemiologica research are treated alike keeping in mind the rules o distributive justice.The welfare of the individual has to b balanced against the welfare of the community and society a large.

Specific Ethical Principles applied to Epidemiology:

1.Informed Consent: When individuals are to be the subject o any epidemiological studies, the purpose and general objectives of the study has to be explained to them keeping in mind thei level of understanding. It needs to be ensured that privacy wil be maintained.

In the context of developing countries, obtaining informed consent has been considered many times as difficult/impracticable/not meeting the purpose on various grounds such as

(a) Whether the subjects or patients , are sufficiently knowledgeable or competent to understand the meaning of informed consent?
(b) Culturally, decision making will be done, not at the individual level but at the level of head of the family or village/community head.

However, **there is no alternative to obtain an informed individual consent.** What should be the contents of the informed consent also becomes a crucial issue. How much to disclose and

the implications of nondisclosure are to be considered seriously.

In spite of obtaining informed individual consent, it is quite likely that the subjects/patients may not be fully aware and may not be aware of their rights. In this context, the role of investigator is crucial and he/she should remain vigilant and conscious of his/her obligations towards the subjects/patients, all through the course of the studies.

2. In most epidemiological research it would be necessary to have the **consent of the community** which can be done through the Village Leaders, the Panchayat *etc.*

3. In obtaining the consent of individuals or communities it is important to keep in mind that working through peer groups or through Panchayat *etc.*, may mean that the individuals or community would feel reluctant to disagree and refuse to give consent because of **societal pressures**. This is something that has **to be carefully avoided.**

4. Particularly in country like India with the level of poverty that is prevalent it is easy to use inducements, especially financial inducements to get individuals and communities to consent. **Such inducements are not permissible.** However, it is necessary to provide for adequate compensation for loss of wages and travel/other expenses incurred for participating in the study.

5. All **risks involved** including the risk of loss of privacy must be explained to the participants in an epidemiological study.

6. The design of the study should ensure that the **benefits of the study are maximised** for the individuals and communities taking part in the study. This means that at the onset itself the investigators should design the way in which the results of the study are going to be communicated and also decide whether individuals identified at particular risk during the course of the studies would be informed. It may also be necessary in some instances to inform the concerned family members about the results. For example, as in AIDS, STD *etc.* It may not always be possible to communicate study results to individuals but research findings and advise should be publicised by appropriate available means. In countries like India it is important that the beneficial results of epidemiological studies are fed into the health system and necessary training modules should be developed as part of the epidemiological project.

7. All attempts should be made to **minimise harm** to the individuals and society at large. Special consideration for the cultural characteristics of the communities which are being studied is essential to prevent any disturbance to cultural sensitivities because of the investigation.

8. **Maintaining confidentiality** of epidemiological data is

absolutely essential A particular concern is the fact that so
population based data may also have implications to issues li
national security and these need to be carefully evaluated at t
beginning.

9. In all situations where there is likely to be **conflicts**
interest it must be ensured that the interest of the individua
involved in the study are protected at all cost.

10. **Scientific Objectivity** should be maintained with honesty a
impartiality, both in the design and conducting study and
presenting and interpreting findings. Selective withholding
data and similar practices are unethical.

11. **Ethical Review Procedures:-** In addition to the Resear
Review Procedures, Ethical Committee has authority a
responsibility for review and approval of research proposals fr
ethical angle. Specific areas to be covered include:-

(a) Plan for informed consent
(b) Assess risks and anticipated benefits
(c) Equitableness
(d) Protecting vulnerable subjects.

In all Ethical Review Committees at least one or t
individuals with an understanding of the principles
epidemiological ethics have to be included. Ethical Committe
should be independent and comprise of epidimiologist
clinicians, statisticians, social scientist, philosopher, leg
expert and representatives from voluntary groups. Members shou
be aware of local, social and cultural norms as this is the mo
important social control mechanism. Ethical Committee membe
should be kept informed as to how the ethical guidelines a
actually being implemented. Regulatory mechanism can come from
core group of the technical monitoring committee which may ref
issues of ethical concern to the ethical committee.

12. **Distinction between research and programme evaluation:** It
important to make a distinction between epidemiological resear
and programme evaluation. In order to evaluate the beneficial
other effects of various health related programmes which a
initiated primarily by Governmental Agencies, Longitudin
epidemiological studies may be necessary. These studies a
slightly different because they are not prospectively evaluati
issues, but looking at the effects of a programme that is alrea
initiated. It is ideal that whenever a programme is launched, t
monitoring and evaluating mechanisms should clearly be planned
the very beginning so that there is no conflict at a later time

Resource Material

1. International Guidelines for Ethical Review
Epidemiological Studies, CIOMS, Geneva, 1991.

GUIDELINES FOR ASSISTED REPRODUCTIVE TECHNOLOGIES IN INDIA

I. TECHNICAL AND SCIENTIFIC ASPECTS

1. INTRODUCTION

The special programme by WHO on human reproduction ha estimated that there are 60 to 80 million infertile couple worldwide. It has also been variously estimated that between 6 10% of the couple are infertile. In India, the stable famil structure and the desire for children is the norm; there is als a social stigma associated with infertility. As a result of thes two there is an ever increasing demand for dignostic an therapeutic interventions in infertile couple. The advent o technologies of Assisted Reproduction have not only enhanced th possibility of pregnancy but have also made women conceive i situations which would have not have been possible a decade ago However many of these technologies require enormous technica expertise and infrastructure, carry a success rate below 30% eve in the best of hands, are expensive, and tax the couple' endurance physically, emotionally and economically. There is a urgent need to draw up necessary guidelines, so that optimu benefit of these newer technologies are made available t appropriate persons by skilled team of experts, at affordabl health and economic cost, at identified facilities for Assiste Reproductive Technology in our country.

2. HISTORICAL PERSPECTIVE

The first report of successful extracorporeal fertilizatio and cleavage of the human egg is that of Rock and Menkin in 1944 Thirty years later the successful extracorporel fertilisation an cleavage of a donor egg and transfer into a recepient uterus wa reported. It was only in 1978 that the first "test-tube baby was born due to the efforts of Edwards and Steptoe. An earlie attempt had resulted in an ectopic pregnancy. In 1979 Schettles reported the intratubal transfer of freshly aspirated oocytes a the time of tubal anastomosis. This had been preceded th following day by cervical insemination. The patient delivere normally at term. In 1983 Tesarik reported the first pregnancy after tubal microsurgery and transfer of oocyte and sperm int the fallopian tube in the same sitting. Asch and workers reported a pregnancy and birth following laparoscopic placement of sperm-oocyte mixture in 1984. Devroey reported the firs pregnancy and birth by the technique of Zygote Intrafallopia Transfer in 1986. With increased success rates of ovaria stimulation, oocyte retrieval and invitro fertilization an development, the problem of dealing with excess oocytes an embryos has been tackled effectively by cryopreservation. Trounson reported the first human pregnancy following thawing o frozen embryos in 1983. Cryopreservation is also of use in case of oocyte donation. Micromanipulation of gametes has bee utilised for those situations with severe male factor, in the presence of previous failed fertilization and in the presence o antibodies impeding sperm-oocyte interaction. The firs pregnancy was reported by this technique in 1988.

3. OBJECTIVE OF THE DOCUMENT

The objective of this document is to standardise and regularise the use of these technologies in our country. Since these technologies are aimed at alleviating the problems of the infertile couple, proper use of this technology is vital.

4. DEFINITION AND SCOPE

Assisted Reproduction is defined as "manipulating the oocyte outside the body and then transfer of gametes or embryos again into the body". The technology covers the following procedures :

i) In vitro fertilisation and embryo transfer (IVF-ET)

ii) Gamete Intrafalloppian transfer (GIFT)

iii) Zygote intrafalloppian Transfer (ZIFT)/Preembryo Transfer/Pronuclear Stage Embryo Transfer (PROST)

iv) Transfer of gamate/embryo and surrogate motherhood.

v) Micromanipulation of gametes

Although strictly speaking only the above categories fit the description of Assisted Reproductive Technologies, other allied techniques are also to be considered because these are often used as a part of management of infertile couples before they are considered for ART. These allied techniques include :

i) Intrauterine insemination

ii) Sperm Intrafallopian Transfer

iii) Sperm Intraovarian Transfer

iv) Intraperitoneal Sperm Transfer

5. SCREENING OF INFERTILE COUPLE

In India most couples marry young. As and when a couple anxious to conceive seek medical help, a simple examination of both the husband and wife should be done irrespective of preceding period of infertility. If menstrual history, sexual history, physical examination findings of the couple and semen analysis report are normal the couple may be reassured, counselled and requested to report back if there is no conception within 2 years of cohabitation (if the age of woman is more than thirty years, then take the period as 1 year of cohabitation. This advise is given mainly to avoid unneccessary investigations and invasive procedures.

Detailed investigations without waiting any further and if required, referral to centres carrying out IVF could be carried out immediately under the following conditions:

- wife is healthy and is more than 35 years of age
- severe endometriosis
- genital tuberculosis
- irreparable damage to or absence of Fallopian tubes
- frozen pelvis
- absence of ovary
- primary ovarian failure - azoospermia, severe oligo asthe no or teratozoospermia, in the husband
- absense of uterus

Preliminary investigations and management for infertil couple can readily be carried out at District Hospitals, Urba Clinics, Medical Colleges and appropriately equipped Privat Clinics. The following minimal investigations need to be carrie out to ascertain the cause of infertility.

Husband: (In 40% of infertile couples male factor is a caus of infertility)

- Physical examination both systemic and local to detec any problem that might be the cause of infertility o modify the management of infertility.

- Semen analysis including both morphological an functional tests should be carried out ; if an abnormality detected repeat tests may be done afte suitable intervals. Abnormal finding on repeated seme examination warrants full scale investigation b appropriate specialist to ascertain the cause an institute necessary treatment.

- Screening for infections including Syphilis, Hepatiti B and HIV and appropriate management.

- If needed appropriate endocrinological investigation and therapy.

Wife :

- Physical examination both systemic and local to detec any problem that might be the cause of infertility o modify the management of infertility.

- Detection and timing of ovulation by BBT, cervica mucus study, ultrasonography, premenstrual endometria biopsy and histopathological examination.

- Assessment of tubal patency by appropriate investigations including Hysterosalpingography, Diagnostic ultrasound, laparoscopy or hysteroscopy i required to find out/ rule out specific problems an to assess response to therapy.

- Screening for local factors including cervical mucus

related problems and lower genital tract infections and instituting appropriate therapy.

- Screening for reproductive tract infections including Syphilis, Chlamydia, Tuberculosis, Hepatitis B and HIV and appropriate management.

- If needed appropriate endocrinological investigations and therapy.

Preliminary screening and management of infertile couple are to be carried out at hospitals/clinics where trained and interested Gynaecologists/Andrologists/Endocrinologists and investigation facilities are available. Once the cause of infertility had been identified, simple management procedure can be taken up by trained Gynaecologist/Andrologist. First line management with appropriate therapy including ovulation induction with or without artificial insemination using husband's semen (repeated atleast upto 6 cycles) should be attempted in such centers and only those couples who are not responding, may then be referred to AR Centres.

6. SELECTION CRITERIA FOR ART

i) Selection Criteria for In Vitro Fertilization and Embryo Transfer (IVF-ET) :

1. Tubal Disease
2. Emdometriosis
3. Unexplained infertility
4. Immunological factors
5. Cervical factor
6. Male factor
7. Ovarian disorders
8. Uterine disorders
9. In association with donor eggs and donor embryos

1. Tubal Disease

I.V.F./E.T. can be offered where microsurgical techniques for tubal and peritoneal disease have failed or are unlikely to benefit the patient. The choice between I.V.F. and Microsurgery would be dictated by the presence of peritubal adhesions, condition of the tubal wall, condition of the ciliary epithelium and degree of fimbrial damage. Patients who have already undergone tuboplasty and those with inaccessible ovaries would be more suitable for I.V.F. In cases of history of ectopic pregnancy, I.V.F. would be a better option.

2. Endometriosis

I.V.F. is a suitable option for women with moderate to severe endometriosis and in those where medical and surgical therapy have failed and sometimes is even offered for mild to moderate endometriosis in the presence of other factors

contributing to infertility.

3. Unexplained infertility

Couples who have prolonged unexplained infertility would benefit from I.V.F. as many factors such as subtle ovulation defects, defects in ovum pick-up, gamete transport, tubal environment, sperm abnormality, oocyte abnormality may come to light when I.V.F. is used.

4. Immunological factor

I.V.F. can be considered when there are antisperm antibodies in the male or the famale and when other techniques such as immunosuppression, use of condoms, intrauterine insemination and other therapeutic measures have failed.

5. Cervical factor

I.V.F. can be offered for cervical factor only if repeated attempts (6 to 8 cycles) of intrauterine insemination have failed and other therapies have not resulted in pregnancy.

6. Male factor

I.V.F.-E.T. is logical therapy in the presence of low concentrations of sperm (less than 10 million/ml.), low motility (less than 30%) and in the presence of abnormal morphology (greater than 60% of abnormal forms as per Yovich). In severe male factor, assisted fertilization by means of Micromanipulation and sperm injection can be offered even in obstructive and non-obstructive cases. No universally accepted minimal sperm concentration for IVF success exists. In severe oligospermia, teratospermia, cryptospermia, azoospermia (obstructive/nonobstructive) intracytoplasmic sperm injection can be employed using either ejaculated or epididiymal sperm.

7. Ovarian disorders

I.V.F. - E.T. can benefit patients with hypogonadotropic anovulation, oligoovulation, and luteal phase deficiency, although IVF is rarely indicated when these disorders exist as isolated conditions. IVF - ET can be used for women with luteinized unruptured follicle syndrome in polycystic ovarian disease.

8. Uterine disorders

Patients with mullerian agenesis, congenital uterine anomalies, and women with severe intrauterine adhesions refractory to surgical lysis of the adhesions as well as hysterectomized patients can, through IVF, transfer their embryos to a surrogate mother.

9. In association with donor eggs and donor embryos

Women who have undergone either premature menopause or timely menopause and women in the perimenopausal age group who do not show proper recruitment of follicles and who have other existing causes of infertility can avail of the option of donor eggs and donor embryos. Also women with genetic disorders, those who have undergone radiation therapy and with ovaries which are not accessible by ultrasound due to severe adhesions can avail of donor eggs.

ii) Selection Criteria for Gamete Intrafallopian Transfer(GIFT):

The experimental background for gamete intrafallopian transfer is the ability of the fallopian tube to serve as the site for capacitation and fertilization in human beings. Earlier experiments by GIFT were carried out on monkeys who had undergone tubal resection and ligation. In 1979 Shettles reported pregnancy after intratubal transfer of freshly aspirated oocytes at the time of tubal reanastomosis combined with cervical insemination. Asch and colleagues reported the first pregnancy and birth using laparoscopic GIFT. Indications are almost similar to that of IVF-ET.

iii) Choosing between IVF - ET & GIFT

Deciding on which technique to utilise must be individualised for each patient. The advantages of IVF over GIFT are documentation of fertilization, less trauma and anaesthetic risk. There is no exposure to excess quantities of carbon dioxide in IVF as happens during laparoscopic insufflation with GIFT. It has been suggested that GIFT is more natural as fertilisation occurs in the tubal ampulla, the gametes are minimally exposed in vitro and early embryo development occurs in a natural environment.

iv) Zygote Intra Fallopian Transfer (ZIFT)

This is an offshoot of the IVF and GIFT procedures where the first pregnancy was reported by Devroey. This procedure entails the transfer of preembryos into the falloppian tube either laparoscopically or by transvaginal retrograde cannulation of the fallopian tubes either by ultrasound or by hysteroscopic guidance.

v) Microassisted Fertilisation

Subzonal insemination (SUZI), Intracytoplasmic Sperm injection (ICSI) and Assisted hatching need micromanupulation of gametes. SUZI involves sperm injection directly into the oocyte outside the body, this is replaced by ICSI which involves injection of sperm into the cytoplasm of the oocyte under certain conditions such as aging ova, in elderly women, repeated failure of implantation at IVF and in male factor infertility. Assisted hatching of embryo by drilling a hole in the zona pelucuda is

resorted prior to embryo transfer for improving implantation rates.

Finally, the choice of the procedure used eg. IVF-ET, GIFT, ZIFT, PROST etc. is made depending upon the needs of the couple, availability of facilities, experience and expertise of the gynaecologist/embryologist.

7. COMPLICATIONS

AR procedures carry a small risk both to the mother and the offspring . It is essential that these risks are defined and explained to the couple and appropriate counsellng done. AR procedures are to be initiated only after they understand these and still want to undergo AR. Some of the most commonly encountered problems include :

1. Multiple Gestation

The reported incidence of multiple gestation range from 20-30 %. Incidence of twin in the range of 10- 20 % may have to be accepted as inevitable but specific efforts are to be made to reduce the incidence of triplets and multple births of higher order. Most of the AR practitioners do not tranfer more than three oocytes for GIFT and more than three embryos for IVF-ET at one sitting ; the remaining embryos, if any, are cryopreserved and if required tranferred at a later cycle.

2. Ectopic Pregnancies

Ectopic pregnancy rates range from 0 to 8% for AR procedures; choice of apppropriate procedure especially in persons with tubal disease may reduce the ectopic pregnancy rates.

3. Spontaneous Abortions

Spontaneous abortion rates range from 20 to 35%. Abortion rates rise with increasing age of the mother and in multiple pregnancies especially presence of three or more foetuses.In cases where more than three foetuses are present many AR experts advise selective embryo reduction.It is essential that the advantages of embryo reduction (better chances of the survival of the other foetuses and the fact that they are likely to be born nearer term, with better birth weight) and disadvantages (the possibility that there might be an increased risk of abortion following the procedure) have to be explained to the couple and then informed consent taken before embryo reduction is attempted.

4. Preterm Births

There is a higher risk of premature/ low birth weight delivery following AR especially in the presence of multiple foetuses.

5. Ovarian Hyperstimulation Syndrome

The use of superovulation for Assisted Reproductive Technology entails the risk of Hyperstimulation for some women (0.2 -8.0%). This is determined by the hormonal profile of the woman, the Estradial values (greater than 2000- pg./ml.), the dose for the trigger of ovulation, the ability to aspirate all the follicles at the time of oocyte retrieval and a host of other factors. The Programme Director should be fully aware of the means of avoiding hyperstimulation and also of treating it. Careful monitoring and management will reduce the risk of this, as well as the morbidity associated with hyperstimulation.

In addition to these specific complications of AR, the persons undergoing various AR procedures incur the risks associated with the operative and anaesthestic procedures involved in AR.

8. FACILITIES

Assisted Reproduction requires the availability of

1. Manpower with expertise and qualifications.
2. Infrastructure such as Equipment/Supplies/Space.

i) Manpower - Expertise and qualifications

The organisation and implementation of an ART programme calls for significant teamwork with close collaboration, coordination and cooperation between concerned and commited clinicians, endocrinologists, ultrasonographists, embryologists and a team of supportive paramedical and laboratory workers. All members of the team should have a commitment to the programme which often calls for irregular working hours and hard work. It is essential that right from the inception of the programme there is clear cut documentation on the responsibilities of each of the team members. The following personnel form an ideal team.

a) Clinical Director (Clinical Science) : The Director is the Team Leader and is overall incharge of the clinical as well as the laboratory aspects of Assisted Reproduction Technology. He or she could be a gynaecologist with adequate training in endoscopy, oocyte retrieval, administration and laboratory and would be required to liaison with the clinical faculty, laboratory faculty, secretary, nurse, anaesthetists, RIA laboratory, psychiatrist and operating room staff. The director should be competent to tackle any emergency arising from clinical situations and in the laboratory. He should be fully aware of use of hazardous material eg. liquid nitrogen. The Director has the following major responsibilities :

- obtaining informed consent for all procedures,
- selection of patients for various Assisted Reproduction procedures,
- the decision to repeat/ change over to other methods/advise

termination of further attempts at AR procedures,
- to tackle any emergency arising from clinical situations and in the laboratory,
- maintanance of records and ensuring confidentiality,
- periodic analysis of data and review of the activities and appropriate corrective measures as and when necessary,
- laison with the state/central govt agencies,
- submission of appropriate data e.g. the pregnancy rates t the Accreditation authority or licensing authority or Registry.

b) Laboratory Director (Basic Science) : Post-graduate i reproductive biology with adequate training and experience in th Andrology and Embryology laboratory, quality control, medi preparation, semen examination and cryopreservation. His administrative duties would include purchase of equipment an supplies, hiring of laboratory personnel and formulate al laboratory policies. His qualifications would be a M.Sc., preferably a Ph.D. and M.D. desirable.

c) Technologists (Lab) : Laboratory personnel trained i media preparation and quality control, serum collection an preparation, maintenance of equipment and supplies, maintenance of log books, performance of quality control, and ability t identify oocytes, fertilization and cleavage (sperm-eg interaction) and semen analysis and preparation procedures. They should be Science graduates with the above skills and also have basic understanding of cultural conditions. The laboratory staff should have adequate protection from blood products and semen. All couples entering the IVF programme should be pre-tested for HIV and Hepatitis-B in order to protect the laboratory personnel.

d) Nurse Coordinator : A qualified Nurse with experience in Gynaecology and Infertility fields. She would be responsible for daily blood collection, obtaining endocrine assay reports, maintenance of equipment in the operation theatre, scheduling of appointments and sonography examinations and assisting in oocyte retrieval and embryo transfer.

e) Counsellor : The role of the counsellor is well acknowledged in the treatment of infertility as clinical research suggests that the infertile couple is at risk for sexual dysfunction, psychiatric co-morbidity and marital conflict. Psychological evaluation and intervention should be offered to couples and should be available on request. The counsellar should be a person with thorough understanding of ART procedures and benefits and problems associated with them. He should be able to give a clear picture about the centre, services offered, cost and present pregnancy rate.

In developed countries specially trained counsellors are usually available and counselling is taken as an essential pre-requisite for couple seeking ART. In the Indian context especially in smaller centres which have just been opened, specific trained counsellor may not be readily available; in such

a situation, the Gynaecologist, Andrologist and Embryologist or the Para medical personnel who had the know- ledge, time, skill, and interest in counselling can be entrusted with the task of counselling the couple. It is essential that every effort should be made to explain the procedures that are going to be used and their consequences to the couple, assess their response and needs before ART procedures are initiated.

f) Secretary : The secretary would be responsible for patient appointments, answering inquiries and letters and administrative duties.

g) Ancillary Services : These would include

- Anaesthetist,
- Radio immunoassay Laboratory and
- Technical staff in the Operation theatre and Laboratory.

The entire programme of ART stresses on the importance of team effort. The individuals have to work dynamically in groups. Professional burnout can occur in this highly and intensely personal technololgy and hence the leader or director of the group has responsibility and privilage of holding the group together.

ii) Equipments , Supplies and Space

a) Space :

The space requirements for isolation of Embryology, Andrology Laboratories and Operation Theatre should be met. These areas should be supplied by clean, filtered, air-conditioned air. Ideally speaking the laboratory should be under a positive pressure environment and should be walled off from other areas. Other rooms would include Interview rooms, Examination room, Sonography room, Recovery room, Patient waiting area, Toilet areas, Waste collection areas, Autoclave room and Semen collection room. The walls in the Operation Theatre and the Laboratory should be easily washable and disinfected. Carpeting is not permitted. Aerosols and pest control should not be used in the Laboratory.

b) Equipments :

The following equipments are mandatory for ART Programme :

i) Horizontal laminar flow hood.
ii) Stereo microscope.
iii) Inverted microscope.
iv) Phase contrast microscope.
v) Water jacketed CO_2 incubator with CO_2 regulator and at least 3 CO_2 cylinders.
vi) Osmometer.
vii) pH meter.

viii) Centrifuge and ultracentrifuge.
ix) Water bath.
x) Analytical balance.
xi) Refrigerator.
xii) Millipore water purification system.
xiii) Stage warmer.
xiv) A Makler Chamber for semen analysis or haematocytometer.

To set up ART lab, cryogenic unit and micromanupulatio equipments are desirable.

c) Supplies :

i) Semen containers.
ii) Tissue culture flasks.
iii) Disposable pipettes.
iv) Culture tubes and Embryo transfer catheters.
v) Oocyte retrieval needles and tubes.
vi) Culture dishes.
vii) Organ culture dishes.
viii) Ultrapore filters.
ix) Microscope slides and cover slips.
x) Rubber bulbs.
xi) pH buffer.
xii) Osmometer fluid.
xiii) Pipette tips.
xiv) Disposable syringes (Liverlock), 1ml, 2ml, 5ml, disposable needles.
xv) Cryopreservation vials and straws.
xvi) Spirit lamp.
xvii) Cartridges for water purification system.
xviii) Tissue culture medium and chemicals associated with preparation of tissue culture media.

Note - All material used in the ART Laboratory should not be toxic to sperm and embryo.

9. COORDINATION, COLLABORATION AND COOPERATION

Assisted Repropductive technology is highly specialised and needs financial, technical and clinical backup. After setting up the facility, its smooth functioning calls for proper liason, understanding and trouble shooting alongwith coordination and cooperation from all areas.

In many metropolitan cities of India the expertise and facilities needed are available in different institutions situated a few kilometers apart and they may be able to work together even though they are all not working under the same roof in the same institution.

The Institutions where the experts from different specialities work, have all the necessary expensive sophisticated equipments. In the existing situation of economic constraints it might be worthwhile to set up AR clinics in an

area where an operation theatre and embryology laboratory are present in the close proximity in the same institution. The infrastructure available in the neigbouring institutions can be utilised optimally for diagnositc procedures needed for AR. This may be the most efficient and cost effective manner in which ART programme may be initiated in India. This arrangement however requires personal commitment of the individuals concerned and the commitment from the respective Institutions that the facilities will be made available on a continuous basis to the couple seeking AR. In such situation, the In-charge shall be Co-ordinator of the Institute, (Director or Dean or person designated as Head)

10. ESTABLISHMENT OF PROTOCOLS AND MAINTENANCE OF RECORDS

All protocols used in the laboratory for I.V.F. and related procedures must be documented and available as manuals. These manuals should be revised periodically. Log books for the maintenance and periodic overhauling of all equipment should be maintained. The entire procedure from the ovarian stimulation protocol to the oocyte retrieval and oocyte and sperm preparation including evaluation of the morpholgy of the gametes, their number, timing of insemination, date of embryo transfer, number of embryos or gametes transfered and the fate of the gametes must be documented. Abnormal pre-embryos such as polyploid embryos should not be transfered. Cryopreserved material must be labelled indexed and stored properly. The laboratory personnel should be well-versed with the techniques of cryopreservation. Batches of culture media must be identified. All agents used in the Laboratory must be entered in a Register and the date of receipt of the reagents entered on the box containing the reagents. Asepsis should be maintained at all times. Each couple undergoing treatment should have a minimal screen for HIV and Hepatitis. Sera of patients used for embryo culture should not be interchanged. The Laboratory personnel should be offered vaccinations for Hepatitis B. Gloves should be worn at all times. Clothes specific for use in the laboratory should be provided. Regular shoes should not be taken into the Laboratory. Preparation of culture media should be done in dedicated containers using ultrapure water and dedicated reagents. The media should be checked for pH and osmolarity. Facilities for proper refrigeration and freezing should be available, back-up of electrical supply and voltage stabilisers should be available in areas prone to electrical failures.

Mouth pipetting is not permissible and only mechanical pipetting is allowed. Eating, drinking, smoking within the precints of the Laboratory should be prohibited. Contaminated material should be disposed off in the proper fashion. Biological material should be handled with care and disposed off after sealing.

It is essential that all documentation regarding every patient treated in the centre is maintained meticulously and all precautions are taken to ensure that confidentiality is

maintained. It is preferable that a networking of the centre involved in ART Programmes are attempted right now when only few centres are doing ART, so that as more and more centres tak up the programme the net work will grow and the Regional ar National data on the ART programme will automatically becom available.

11. ACCREDITATION

It is estimated that at the moment there are about 5 centres offering AR in India. Some have been well establishe and have been functioning for some years. Others are in variou stages of being established.

In order to ensure quality of care it is imperative that proper accreditation procedure is followed in establishement o AR centres. All AR centres should follow standardised protocol and guidelines. There should be a strict internal and externa quality control programme for all AR centres. A team consistin of gynaecologists, embryologists, andrologists, legal and ethica experts along with the social scientists may be included in th accreditation committee.Representatives of various professiona bodies in the specialities connected with AR procedures such a the Federation of Obstetric and Gynaecological Societies of Indi (FOGSI) and Indian Society for Assisted Reproduction (ISAR) ma also be included in the accreditation committee. In addition th opinion of these professional bodies and organisations such a Indian Council of Medical Research (ICMR) and Drug Controller o India (DCI) should be saught on the recommendations of th accreditation committee.

The aim of the accreditation procedure is to ensure that :

- the institutions providing AR do maintain the qualit of care expected
- infertile couple get good quality care and are no exploited
- the institutions offering AR do get the needed suppor especially in terms of streamlined procedures fo import of needed drugs, reagents and equipment.

Appropriate expert panel would inspect the AR centres as part of accreditation procedure before the centre i operationalised and also periodically after it starts functioning. The accreditation committee will review the existin infrastructure and facilities, the track record of the centre the upkeep of the records, security arrangements for gamete embryo storage and maintanance of the confidentiality and mak their recommendations to the appropriate authorities . Appropriate legal/executive procedures for providin accreditation to these centres will have to be evolved an implementing agencies identified. AR Centres require read access to reagents, drugs and equipment many of which have to b

imported in order to provide patient care. Steps may have to be evolved to assist accreditted ART centres by streamlining the procedures that these centres have to adapt for import, so that their requirements are met without undue delay and additional expenses.

Some of the accreditted centres can be utilised for training postgraduates or interested specialists from the related specialities so that in a phased manner AR facility becomes more widely available in the country. Some of the accreditted ART centres could also take up research studies on specific aspects of AR based on approved protocols.

12. REGISTRY

A national registry pertaining to all centres who are accredited by the licensing authority should be maintained and should contain records of treatment cycles and outcome.

II. ETHICAL AND LEGAL ASPECTS OF ASSISTED REPRODUCTIVE TECHNOLOGIES

1. GENERAL ETHICAL AND LEGAL ASPECTS

There is a certain element of risk associated with AR procedures. It is therefore necessary to ascertain the therapeutic value of the AR procedure in each case.

1.1 Informed Consent

After duly counselling the couple/oocyte/semen donor, an informed and written consent should be taken from both the spouses as well as the oocyte donor, as the case may be. They should be explained the various risk factors associated with the procedures in simple language and the words that they can understand. These include risks associated with ovarian hyperstimulation, anaesthestic procedures, invasive procedures like laparoscopy, aspiration of ovum. They should also be explained the possibility of multiple pregnancies, ectopic gestation, increased rate of spontaneous abortion, premature births, higher perinatal and infant mortality as well as growth and developmental problems.

1.2 Selection of Donor

The doctor assumes the responsibility in selection of the suitable donor in terms of following:

* Complete physical examination of the donor should bedone to ascertain the good health of the donors of semen, oocyte or embryo.

* The donor should be healthy with a good quality eggs or sperms and preferably with proven fertility record.

* The physical characteristic and mental make-up of the donor should match as closely as possible to that of the spouse of the recipient, specially with reference to colour of the skin, eyes and hair, height and build, religious and ethnic background, the educational level and ABO blood type.

* Blood group of the proposed donor and donee should be tested with respect to Rh compatibility.

* No person suffering from any sexually transmitted disease (e.g. syphilis, gonorrhea, chlamydia, herpes, HIV etc.), infectious disease (e.g. hepatitis - B, HIV) or genetically transmissible disease should be used as donor.

* Sexually transmitted diseases should be ruled out not more than one week before the seminal fluid is obtained. It is preferable that donated semen is cryo-preserved and used only after 6 months as this would enable the centre to retest the donor after 3 months for HIV and eliminate the potential risk of HIV transmission in the 'window' period of HIV infection.

* Identity of the donor as well as the recipient should be protected from each other. However all the records of the donor must be preserved in order to trace him/her in case of any eventuality and should be confidential.

* Confidentiality of the entire procedure and its outcome is advisable and therefore no relative should be accepted as a sperm donor besides avoiding the claims of parenthood and inheritance rights.

* Written consent of the donor should be taken towards unrestricted use of sperms or oocytes for AR, as well as an undertaking from him/her that he/she will not attempt to seek the identity of the recipient. In case of the donor is married, to take the written consent of the spouse, if possible.

* It is also desirable to restrict the use of semen from the same donor to 10 pregnancies to avoid the possibil ity of an incestuous relationship occurring among the offsprings at a later date.

* In case of the oocyte donor, incurring any health problems during the process of donation, the costs of the subsequent health care should be borne by the potential recipient couple irrespective of whether they receive oocyte donation as planned or not. *In case of unused surplus embryos, consent of the concerned couple should be obtained to cryopreserve such embryos for donation to other needy couples. Such embryo donations should be kept anonymous.

2. SPECIFIC ETHICAL AND LEGAL ISSUES INVOLVED IN ART

2.1 Legitimacy of the Child born through ART

A child born through AR is presumed to be the legitimate child of the couple having been born within the wedlock and with consent of both the spouses with all the attendant rights of parentage, support and inheritance. Sperm/oocyte donor should have no parental right or duties in relation to the child and their anonymity should be protected.

2.2 IVF-ET and Surrogate Motherhood

There are no medicolegal problems posed by IVF-ET with egg and sperm of married couple. With either egg or sperm donated, it is governed on the same lines as AID with the married partner being the natural or biological mother. IVF-ET with donated egg or sperm or womb leasing will create two to three sets of parents, genetic, biological and natural. Following consensus has emerged universally with respect to surrogate motherhood:

1. Surrogate motherhood should be legal only when it is coupled with authorized adoption.

2. It should be rebuttably presumed that a woman who carries the child and gives birth to it is its mother.

3. The intending parents should have a preferential right to adopt the child subject to six week's postpartum delay for necessary maternal consent.

4. It should be legal only if medically certified as the only solution to infertility or any other medical bar on pregnancy, by the intending mother.

5. It should be supervised by a qualified consultant to enforce adequate genetic screening.

6. The contract for surrogacy despite reasonable payment of compensation on completion of adoption would be valid subject to surrogate's right to retain the baby if she so desires. The only remedy for the genetic father then would be to claim for custody on the grounds of the best interest of the child.

7. Abortion under the Abortion Law on the medical ground should be an inviolate right of the surrogate and the adopting parents have no claim over the amounts already paid.

2.3 Adultery in case of AID

AID in a married woman with the consent of the husband does not amount to adultery on part of the wife or the donor, as there is no sexual intercourse involved. AID without the husband's consent can be ground for divorce or judicial separation.

2.4 Consummation of Marriage in case of AIH

Conception of the wife through AIH does not necessaril amount to consummation of marriage and a decree of nullity woul still be granted in favour of the wife on the ground of impotenc of the husband or his willful refusal to consummate the marriage However, such a decree could be excluded on the grounds o approbation.

2.5 Rights of An Unmarried Woman to AID

There is no legal bar on an unmarried woman going for AID However, universally it is recommended that AID should b performed only on married women and that too with the writte consent of her husband, two parent family being always better fo the child whose interests will always outweigh all othe interests. Besides, child born to a single woman through AID i deemed to be illegitimate.

2.6 Posthumous AIH through Sperm Bank

Though the Indian Evidence Act, 1872 says that a child bor within 280 days after dissolution of marriage (by death o divorce) is a legitimate child since that is considered to be th gestation period, it is pertinent to note that this Act wa enacted as far back as 1872 when one could not even visualis ART. The law needs to take note of these advancements. A chil born to a single woman is already not in a very happy position in our society specially; why doubly damn him by branding him a illegitimate? Considered opinion is that a child born to woman with the sperms of her deceased husband artificiall inseminated should be considered to be a legitimate chil notwithstanding the existing law of presumptions under ou Evidence Act. The law needs to move alongwith medica advancements and suitably amended so that it does not give ris to dilemnic or harsh situations.

2.7 Preservation, Utilisation and Destruction of Embryos

While passing The Human Fertilisation and Embryology Act 1990, the British Parliament accepted the Warnock Committee recommendations prohibiting research on or keeping alive any live embryo over 14 days after fertilisation, excluding the perio during which the embryo was frozen with maximum storage period of 10 years and a 5 yearly review of semen and embryos deposits. Under this law, early this month nearly 3000 frozen embryos were destroyed in the UK after the expiry of 5 year statutory limit and no consent coming forth from the parents to extend the limit by further 5 years.

In a case of dispute arising between the couple since divorced, after the preservation of embryos, over the right of the woman to conceive the child and seeking custody of the embryos, a recent judgement has gone in favour of the woman, the

husband having consented to the conception at the time of fertilisation. However, the child born in such a case would be deemed to be an illegitimate child.

Resource Material

- Guidelines for Human Embryology and Andrology Laboratories. Fertility & Sterility.October 1992, Supplement 1, vol.58, No.4 (1S & 11S).

- Guidelines for Gamete Donation. Fertility & Sterility February, 1993, vol.59, No.2 (1S & 5S).

- Human Fertilisation and Embryology Authority : Code of Ethics, London, 1993.

- Ontario Law Reform Commission's Report on Human Artificial Reproduction - Related Matters of Canada.

- American Fertility Society's Ethics Committee Report "Ethical Considerations of the New Reproductive Technologies" 1986 and 87.

3. SAMPLE CONSENT FORMS FOR AR PROCEDURES

3.1 CONSENT FORM

We, Mr. _____ and Mrs. _____ hereby give consent to donate sperms of Mr. _____ to Mrs. _____ for purpose of artificial insemination with donor's sperms and we agree that we will have no legal claim on the baby born to Mrs. _____ by the above procedure of artificial insemination.

Mr.

Mrs.

DONOR

SPERM DONATION

3.2 CONSENT FORM

We, Mrs._____ and Mr. _____ state that we are lawfully married and have no children. We desire that Mrs. _____ should be artificially inseminated with donor sperms as we are both desirous that we should have a child by that means. The procedure of artificial insemination has been explained to us and we hereby give consent to such artificial insemination.

I, hereby request you to inseminate my wife Mrs._____.

I, Mr._____ will take responsibility of bringing up the child born by my wife Mrs. _____ as above procedure.

Mr.

Mrs.

RECIPIENT

ARTIFICIAL INSEMINATION

3.3 CONSENT FORM

We, Mrs._____ and Mr. _____ state that we are lawfully married and have no children. We desire that Mrs. _____ should be artificially inseminated as we are both desirous that we should have a child by that means. The procedure of arftificial insemination has been explained to us and we hereby give consent to such artificial insemination.

We agree that identity of the donor for the purpose of such insemination is not to be disclosed to us. We ourselves are not able to procure such donor and agree to accept such donor for the purpose as you may procure. We understand that since fresh samples may be used, small risk of getting AIDS infections cannot be ruled out.#

Mr.

Mrs.

RECIPIENT
ARTIFICIAL INSEMINATION WITH
UNKNOWN DONOR

 # All ART Centres should only use frozen sperms

3.4 CONSENT FORM

This is to certify that I _____ and my husband _____ hereby give consent to donate my oocytes to any infertile couple who wishes to receive them.

The procedure of oocyte collection is explained to us in detail and I understand the risk involved in the procedure as well as premedications and protocols for monitoring of ovulation induction.

The identity of recipients of the oocytes will remain unknown to us and we will not have any claim on offsprings that will be produced by donation of my oocytes.

Mrs.

Mr.

(Signature)

DONOR

OOCYTE DONATION

3.5 CONSENT FORM

We, Mrs._____ and Mr. _____ state that we are lawfully married and have no children. We desire that Mrs. _____ should have IVF-ET/GIFT by oocyte/embryo donation as we are both desirous that we should have a child by that means. The procedure of IVF-ET/GIFT has been explained to us and we hereby give consent to such treatment.

We agree that identity of the donor for the purpose of oocyte/embryo donation is not to be disclosed to us. We ourselves are not able to procure such donor and agree to accept such donor for the purpose as you may procure.

Mrs.

Mr.

(Signature)

RECIPIENT

OOCYTE/EMBRYO DONATION

3.6 CONSENT FOR EMBRYO REDUCTION

We, Mr. & Mrs._____

hereby give fully informed consent for the procedure of Embryo Reduction, to attempt the reduction, of our _____ to _____.

We have been informed that this procedure can lead to the termination of the whole pregnancy or failure to reduce the number of embryos to the desired number of continuation of the pregnancy with the original number of embryos.

We do not hold the doctors responsible for any other future complications in this pregnancy.

We have been explained that since this procedure is done in the first trimester, therefore it is not possible to detect the future anatomical or functional abnormalities of the embryos and therefore a selective reduction may not be possible.

We solemnly pledge that we are giving this consent without any pressure and with full awareness of the consequences.

Mr.

Mrs.

(Signature)

3.7 CONSENT FORM FOR SURROGATE MOTHER

We, Mrs. _____ and Mr. _____ state that we are lawfully married. We give consent that Mrs. _____ should have IVF/ET by embryos of Mrs. _____

The procedure of IVF/ET has been explained to us and we hereby give consent to such treatment.

We agree that we will have no legal claim on the baby born by that procedure and we will hand over the child to the genetic parents on birth of the baby.

Mrs. _____ is volunteering to become surrogate mother purely to help Mrs. _____ .

Mr.

Mrs.

(Signature)

SURROGATE MOTHER

3.8 CONSENT FORM : Participation in IVF Program

Note : This Consent Form should be signed at the time of the initial consultation with the IVF team.

1. I hereby authorize and direct Dr. _____ _____ and such assistants as may be selected by him/her to administer to and treat me _____ in accordance with the attached IVF protocol, which have been discussed with me, and I here by consent to such treatment.

2. I understand that the purpose of my participation in the program is to attempt to become pregnant by means of in vitro fertilization, and embryo transfer because I have been unable to become pregnant due to conditions which have not been, treatable by other currently available methods and procedures.

3. I understand from my reading of the attached IVF brochure and counselling by the IVF team physician that the following is an outline of the IVF process and procedures which will be followed during my participation in the programme :

   a. Administration of medications to assist my ovulation.

   b. Frequent blood tests, pelvic examinations and ultrasound studies to determine development of ovulation.

   c. Admission to the hospital for a laparoscopy or ultrasound retrieval when my ovulatory process is at the appropriate state, as determined by the IVF team, in order to obtain as many eggs as possible from my ovaries (usually one to four).

   d. Mixture of my eggs with my husband's sperm to attempt to allow fertilization, to occur.

   e. Transfer of my fertilized egg into a different medium outside the uterus for growth.

   f. Transfer of the embryo(s) into my uterus by means of a small plastic tube following several cell divisions.

   g. Frequent blood tests through the remainder of my cycle to determine hormone levels and whether pregnancy has occured.

4. I am advised of all the reasonably known risks and consequences associated with this treatment. Those reasonably known risks and consequences have been fully explained to me.

5. I am advised that there are no guarantees that I will become pregnant through my participation in the IVF program or that, if I do achieve pregnancy, a successful full-term pregnancy will result.

6. I understand that the factors that may prevent my becoming pregnant or carrying a fetus to full-term during my participation in the IVF program include, but are not limited to, the following:

   a) The time of ovulation may not be accurately predictable, or ovulation may not occur in the monitored cycle, thereby precluding any attempt at obtaining an egg.

   b) The attempt to obtain an egg may be unsuccessful.

   c) My husband may be unable to obtain a semen specimen.

   d) Fertilization or splitting of the egg outside the uterus may fail to occur.

   e) A laboratory accident may result in the loss of an egg.

   f) Following successful establishment of pregnancy, there is the possibility of miscarriage, ectopic pregnancy (tubal pregnancy), or stillbirth.

7. I understand that should I carry the fetus to full-term, there are no guarantees that congenital anomalies (birth defects) will not occur.

8. I understand that the chances of multiple pregnancy are higher by this procedure than by natural conception.

9. I understand that there is indication in the scientific literature that the occurrence rate of any of the events stated in paragraph 6(f) or 7 is increased or decreased by the procedure.

10. I understand that according to information currently available from other in vitro fertilization centers, pregnancies resulting from the procedure occur at a maximum of 20 percent per cycle attempted. I also understand that the Fertility Clinic program does not guarantee that its success rate will be similar to that of other programs.

11. I understand that I am free to discontinue participation in the program at any time, either verbally or in writing, and that my decision to discontinue will in no way prejudice other treatment that I may receive from the Fertility Clinic. I also understand that if I decide to discontinue participation in the IVF program, I will be responsible for all expenses incurred during the periods of time prior to such discontinuation and which relate to my treatment in the program.

12. I understand that this consent extends from the original period of my participation in the program until the program is completed or until I decide to discontinue participation.

13. I understand that should the results of my treatment or any aspect of it be published in medical or scientific journals, all possible precautions will be taken to protect my anonymity. I grant permission to the IVF team to publish in professional journals statistics relating to my case, provided my name is not used.

Date : _____ Patient:_____

Time : _____ Spouse : _____

Witness :_____ Physician Obtaining Consent :

_____

PART C

APPENDICES

1. Code of Ethics of the Medical Council of India
2. The Nuremberg Code
3. World Medical Association - Declaration of Helsinki

Code of Medical Ethics framed under section 33 of the Indian Medical Council Act 1956

At the time of registration, each applicant shall be given a copy of the following declaration by the Registrar concerned and the applicant shall read and agree to abide by the same:

DECLARATION

1. I solemnly pledge myself to consecrate my life to the service of humanity.
2. Even under threat, I will not use my medical knowledge contrary to the laws of humanity.
3. I will maintain the utmost respect for human life from the time of conception.
4. I will not permit considerations of religion, nationality race party politics or social standing to intervene between my duty and my patient.
5. I will practise my profession with conscience and dignity.
6. The health of my patient will be my first consideration.
7. I will respect the secrets which are confided in me.
8. I will give to my teachers the respect and gratitude which is their due.
9. I will maintain by all means in my power, the honour and noble traditions of medical profession.
10. My colleagues will be my brothers.

I make these promises solemnly, freely and upon my honour.

CODE
General Principles

1. Character of the Physician. The prime object of the medical profession is to render service to humanity; reward of financial gain is a subordinate consideration. Who-so-ever chooses this profession, assumes the obligation to conduct himself in accord with its ideals. "A physician should be an upright man, instructed in the art of healings". He must keep himself pure in character and be diligent in caring for the sick. He should be modest, sober, patient, prompt to do whole duty without anxiety; pious without going so far as superstition conducting himself with propriety in his profession and in all the actions of his life.

2. The physician's responsibility. The principle objective of the medical profession is to render service to humanity with full respect for the dignity of man. Physicians should merit the confidence of patients entrusted to their care, rendering to each a full measure of service and devotion. Physician should try continuously to improve medical knowledge and skill and should make available to their patients and colleagues the benefits of their professional attainments. The physician should practice methods of healing founded on scientific basis and should not associate professionally with anyone who violates this principle. The honoured ideals of the medical profession imply that the responsibilities of the physicians extend not only to individuals but also to society.

3. Advertising. Solicitation of patients directly or indirectly, by a physician, by groups of physicians or by institutions or organisations is unethical. A physician shall not make use of or aid or permit others to make use of him (or his name) as subject of any form or manner of advertising or publicity through lay channels either alone or in conjunction with others which is of such a character as to invite attention to him or to his professional position, skill, qualification, achievements, attainments, specialities, appointments, associations, affiliations or honours and/or of such character as would ordinarily result in his self aggrandisements nor shall he give to any person who-so-ever, whether for compensation or otherwise, any approval, recommendation, endorsement, certificate, report or statement with respect of any drug, medicine, nostrum remedy, surgical, or therapeutic article, apparatus or appliance or any commercial product or article with respect of any property, quality or use thereof or any test demonstration or trial thereof, for use in connection with his name, signature, or photograph in any form or manner of advertising through lay channels nor shall he boast of cases, operations cures or remedies or permit the publication of report thereof lay channels. A medical practitioner is permitted a formal announcement in press regarding the following:

(1) On starting practice.
(2) On change of type of practice.
(3) On changing address.
(4) On temporary absence from duty.
(5) On resumption of another practice.
(6) On succeeding to another practice.

4. Payment of professional services. The ethical physician, engaged in the practice of medicine, limits the sources of his income received from professional activities to service rendered to the patient. Remunerations received for such services should be in the form and amount specifically announced to the patient at the time the service is rendered. It is unethical to enter into a contact of "no cure no payment".

5. Patent and copy rights. A physician may patent surgical instruments, appliances and medicine or copy right applications methods and procedure. The use of such patents or copy right or the receipt of remuneration from them which retards or inhibits research or restricts the benefits derivable therefrom are unethical.

6. Running an open shop (dispensing of drugs and appliances by physicians). A physician should not run an open shop for sale of medicine for dispensing prescriptions prescribed by doctors other than himself or for sale of medical or surgical appliances It is not ethical for a physician to prescribe or supply drugs, remedies or appliances as long as there is no exploitation of the patient.

7. Rebates and commission. A physician shall not give, solicit, or receive nor shall he offer to give, solicit or receive any gift, gratuity, commission or bonus in consideration or return for the referring, recommending or procuring of any patient for medical, surgical or other treatment. A physician shall not directly or be any subterfuge participate in or by a party to act of division, transference, assignment, subordination, rebating, splitting or refunding of any fee for medical, surgical or other treatment.

The provisions of this para shall apply with equal force to the referring, recommending or procuring by a physician or any person, specimen or material for diagnostic, or other study or work. Nothing in this section, however, shall prohibit payment of salaries by a qualified physician to other duly qualified person rendering medical care under his supervision.

8. Secret remedies. The prescribing or dispensing by a physician of secret medicines or other secret remedial agents of which he does not know the composition, or the manufacture or promotion of their use is unethical.

9. Evasion of legal restrictions. The physicians will observe the laws of the country in regulating the practice of medicine and will not assist others to evade such laws. He should be cooperative in observance and enforcement of sanitary laws and regulations in the interest of public health. A physician should observe the provisions of the State Acts like Drugs Act, Pharmacy Act, Poisons Act and Dangerous Drugs Act and such other Acts, Rules, Regulations made by the Central Govt./State Govts. or local Administrative Bodies for protection and promotion of public health.

Duties of Physicians to their Patients

10. Obligations to the sick. Though a physician is not bound to treat each and every one asking his services except emergencies for the sake of humanity and the noble traditions of the profession. he should not only be ever ready to respond to the calls of the sick and the injured, but should be mindful of the high character of his mission and the responsibility he incurs in the discharge of his professional duties. In his ministrations, he should never forget that the health and the lives of those entrusted to his care depend on his skill and attention. A physician shcuid endeavour to add to the comfort of the sick by making his visits at the hour indicated to the patients.

11. Patience, delicacy and secrecy. Patience and delicacy should characterize the physician. Confidence concerning individual or domestic life entrusted by patients to a physician and defects in the disposition or character of patients observed during medical attendance should never be revealed unless their revelation is required by the laws of the State. Sometimes, however, a physician must determine whether his duty to society requires him to employ knowledge, obtained through confidences to him as a physician, to protect a healthy person against a communicable disease to which he is about to be exposed. In such instance, the physician should act as he would desire another to act toward one of his own family in like circumstances.

12. Prognosis. The physician should neither exaggerate nor minimize the gravity of a patient's concition. He should assure himself that the patient, his relatives or his responsible friends have such knowledge of the patient's condition as will serve the best interests of the patient and the family.

13. The patient must not be neglected. A physician is free to choose whom he will serve. He should, however, respond to any request for his assistance in an emergency or whenever temperate public opinion expects the service. Once having undertaken a case, the physician should not neglect the patient, not should he withdraw from the case without giving notice to the patient, his relatives or his responsible friends sufficiently long in advance of his withdrawal to allow them to secure another medical attendant. No provisionally or fully registered medical practitioner shall wailful commit an act of negligence that may deprive his patient or patients from necessary medical care.

Duties of the Physician to profession at large

14. Upholding the honour of the profession. A physician is expected to uphold the dignity and honour of his profession

15. Membership in medical society. For the advancement of his profession, a physician should affiliate with medical societies and contribute his time, energy and means so that these societies may represent the ideals of the profession.

16. Safeguarding the profession. Every physician should aid in safeguarding the profession against admission to it of those who are deficient in moral character or education. Physician should not employ in connection with his professional practice any attendant who is neither registered not enlisted under the Medical Acts in force and should not permit such persons to attend, treat or perform operations upon patients in respect of matters regarding professional discretion or skill as it is dangerous to public health.

17. Exposure of unethical conduct. A physician should expose, without fear or favour, incompetent or corrupt, dishonest or unethical conduct on the part of members of the profession. Questions of such conduct should be considered, first before proper medical tribunals in executive sessions or by special or duly appointed committees on ethical relations, provided such a course is possible and provided also that the law is not hampered thereby. If doubt should arise as to the legality of the physician's conduct, the situation under investigation may be placed before officers of the law, and the physician investigators may take the necessary steps to enlist the interest of the proper authority.

Professional Services of Physicians to each other

18. Dependence of physicians on each other. There is no rule that a physician should not charge another physician for his service, should cheerfully and without recompense give his professional services to physicians or his dependents if they are in his vicinity.

19. Compensation for expenses. A physician should consider it as a pleasure and privilege to render gratuitous service to all physicians and their immediate family dependents. When a physician is called from a distance to attend or advice another physician or his dependents, reimbursement should however be made for travelling and other incidential expenses.

Duties of Physician in consultation

20. Consultation should be encouraged. In case of serious illness, especially in doubtful or difficult conditions the physician should request consultation.

21. Consultation for Patient's Benefit. In every consultation, the benefit
the patient is first importance. All physicians interest in the case should
candid with the patient, a member of his family or responsible friend.

22. Punctuality in consultation. Utmost punctuality should be observed by
physician in meeting for consultation.

23. Conduct in consultation. In consultations no insincerity, rivalry or en
should be indulged in. All due respect should be observed towards th
physician in-charge of the case and no statement or remark be made, whic
would impair the confidence reposed in him. For this purpose no discussio
should be carried on in the presence of the patient or his representatives.

24. Statement to patient after consultation. (a) All statements of the patie
or his representatives should take place in the presence of all the physician
consulting, except as otherwise agreed; the announcement of the opinion to th
patient or his relations or friends shall rest with the medical attendant.

(b) Differences of opinion should not be divulged unnecessarily bit whe
there is irreconcilable difference of opinion the circumstances should be frankl
and impartially explained to the patient or his friends It would be open to ther
to seek further advice should they so desire.

25. Treatment after consultation. No decision should restrain the attendin
physician from making such subsequent variations in the treatment an
unexpected change may require, but at the next consultation, reasons for th
variations should be stated. The same privilege, with its obligations, belongs to
the consultant when sent for in an emergency during the absence of attendin
physician. The attending physician may prescribe at any time for the patient, the
consultant only in case of emergency.

26. Consultant not to take charge of the case. When a physician has beer
called as a consultant, none but the rarest and most exceptional circumstances
would justify that consultant taking charge of the case. He must not do so
merely on the solicitation of the patient or friends.

27. Patients referred to specialists. When a patient is referred to a specialist
by the attending physician, a statement of the case should be given to the
specialist, who should communicate his opinion in writing in a closed cover
direct to the attending physician.

Duties of physician in cases of interference

28. Appointment of substitute. Whenever a physician requests another physician to attend his patients during his temporary absence from his practice, professional courtesy requires the acceptance of such appointment in consistent with his other duties. The physician acting under such an appointment should give the utmost consideration to the interests and reputation of the absent physician. All such patients should be restored to the care of the latter upon his return.

29. Visiting another physician's case. A physician called to visit a patient who has recently been under the care of another physician in the same illness, should not take charge of, nor prescribe for such patient except in case of emergency when he should communicate to the former explaining the circumstances under which the patient was seen and treatment given, or when the physician has relinquished his case, or when the patient has notified such physician to discontinue his services.

When it becomes the duty of a physician occupying an official position to see and report upon an illness or injury, he should communicate to the physician in attendance so as to give him an option of being present. The medical officer should avoid remarks upon the diagnosis of the treatment that has been adopted.

30. Engagement for an obstetric case. If a physician agrees to attend a woman during her confinement, he must do so. Inability to do so on an excuse of any other engagement is not tenable except when he is already engaged on a similar or other serious case. When a physician who has been engaged to attend an obstetric case is absent and another is sent for and delivery accomplished, the acting physician is, entitled to his professional fees, but should secure the patient's consent to resign on the arrival of the physician engaged.

Duties of physician to the public

31. Physician as citizens. Physicians, as good Citizens, possessed of special training should advise concerning the health of the community wherein they dwell. They should bear their part in enforcing the laws of the community and in sustaining the institutions that advance the interests of humanity. They should operate especially with the proper authorities in the administration of sanitary laws and regulations.

32. Public health. Physicians, especially those engaged in public health work, should enlighten the public concerning quarantine regulations and measures for the prevention of epidemic and communicable diseases. At all times the physician should notify the constituted public health authorities of every case of communicable disease under his care, in accordance with the laws, rules and regulations of the health authorities. When an epidemic prevails, a physician must continue his labour without regard to the risk to his own health.

33. Pharmacists. Physicians should recognize and promote the practice of pharmacy as a profession and should recognise the cooperation of the pharmacist in education of the public concerning the practice of ethical and scientific medicine.

DISCIPLINARY ACTION

1. The Medical Council of India desires to bring to the notice of the registered medical practitioners the following statement upon offences and form of professional misconduct, which may be brought before the appropriate Medical Council for disciplinary action in view of the authority conferred upon the Medical Council of India and/or State Medical Councils as provided under Indian Medical Council Act, 1956, or State Medical Councils Acts as may be subsequently amended.

2. The appropriate Medical Council may award such punishment as deemed necessary or may direct the removal altogether or for a specified period from the Register, the name of any registered practitioner who has been convicted of any such offence as implied in the opinion of the Medical Council of India and/or State medical Councils, a defect of character or who after an enquiry at which opportunity has been given to such registered practitioner to be heard in person or by pleader, has been held by the appropriate Medical Council to have been guilty of serious professional misconduct. The appropriate Medical Council may also direct that any name so removed shall be restored.

3. It must be clearly understood that the instances of offences and of professional misconduct which are given do not constitute and are not intended to constitute a complete list of the infamous acts which may be published by erasure from the Register, and that by issuing this notice the Medical Council of India and/or State Medical Councils are in no way precluded from considering and dealing with any form of professional misconduct on the part of a registered practitioner. Circumstances may and do arise from time to time in relation to which there may occur questions of professional misconduct which do not come

within any of these categories. Every care should be taken that the code is not violated in letter or spirit. In such instances as in all others, the Medical Council of India and/or State Medical Councils have to consider and decide upon the facts brought before the Medical Council of India and/or State Medical Councils.

LIST

1. Adultery or improper conduct or association with a patient. Any medical practitioner, who abuses, his professional position by committing any adultery or improper conduct with a patient or by maintaining an improper association with a patient, is liable for disciplinary action as provided under the Indian Medical Council Act, 1956 and/or State Medical Acts, as may be subsequently amended.

2. Conviction by Court of Law for offences involving moral turpitude.

3. Professional certificates, Reports and other Documents. Registered practitioners are in certain cases bound by law to give, or may from time to time be called upon or requested to give certificates, notification, reports and other documents of kindred character signed by them in their professional capacity for subsequent use in the courts of justice or for administrative purposes etc.

(i) Such documents include among other certificates, notifications, reports -

(a) Under the acts relating to birth, death or disposal of the dead.
(b) Under the Acts relating to Lunacy and Mental Deficiency and the rules made thereunder.
(c) Under the Vaccination Acts and the regulations made thereunder.
(d) Under the Factory Acts and the regulation made thereunder.
(e) Under the Education Acts.
(f) Under the Public Health Acts and the order made thereunder.
(g) Under the Workmen's Compensation Act.
(h) Under the Acts and order relating to the notification of infectious diseases.
(i) Under the Employee's State Insurance Act.
(j) In connection with sick benefit insurance and friendly societies.
(k) Under the Merchant shipping Act.
(l) For procuring the issuing of passports.
(m) For excusing attendance in courts of Justice, in public services, in public offices or in ordinary employments.
(n) In connection with Civil and Military matters.
(o) In connection with matters under the control of Ministry of the pensions.

(ii) Any registered practitioner who shall be shown to have signed or given under his name and authority and such certificate, notification, report of document of a kindred character which is untrue, misleading or improper relating to the several matters above specified or otherwise, is liable to have his name erased from the Register.

(iii) A Registered medical practitioner shall maintain a Register of Medical Certificates giving full details of certificates issued. When issuing a medical certificate always enter the identification marks of the patient and keep a copy of the certificate. So not omit to note down the signature or thumb-mark, address and identification marks of the patient on the medical certificate or report.

4. Contravening the provisions of the Drugs Act and regulation made thereunder.

5. Selling Schedule poison to the public under the cover of his own qualification except to his patient.

6. Performing or enabling unqualified person to perform an abortion or any illegal operation for which there is no medical, surgical or psychological indication.

7. A physician should not issue certificates of efficiency in modern medicine to unqualified or non-medical person.

(Note: The foregoing does not apply so as to restrict the proper training and instruction of bonafide students, legitimate employees of doctors, midwives, dispensers, surgical attendants, or skilled mechanical and technical assistants under the personal supervision of physicians).

8. A physician should not contribute to the lay press articles and give interviews regarding diseases and treatments which may have the effect of advertising himself or soliciting practices, but is open to write to the lay press under his own name on matters of public health hygienic living or to deliver public lectures, give talks on the radio broadcast for the same purpose and send announcement of the same to the lay press.

9. As institution run by a physician for a particular purpose such as a maternity home, a sanatorium, a house for the crippled or the blind, etc. may be advertised in the lay press, but such advertisements should not contain anything more than the name of the institution, type of patients admitted, facilities offered

and the residential fees. Name of either the superintendent or the doctor attending should not appear in the advertisement.

10. It is improper for a physician to use an unusually large signboard and write on it anything other than his name, qualifications obtained from a University or a statutory body, titles and name of his speciality. The name should be the contents of his prescription papers. It is improper to affix a sign-board on a chemist's shop or in places where he does not reside or work.

11. Do not disclose the secrets of a patient that have been learnt in the exercise of your profession. Those may be disclosed only in a Court of Law under orders of the presiding judge.

12. Refusing on religious grounds alone to give assistance in our conduct of sterility, birth control craniotomies on living children and therapeutic abortions when there is medical indication; unless the medical practitioner feels himself/herself incompetent to do so.

13. Before performing an operation the physician should obtain in writing the consent from the husband or wife, parent or guardian in the case of a minor, or the patient himself as the case may be. In an operation which may result in sterility the consent of both husband and wife is needed.

14. Do not publish photographs or case reports of your patients in any medical or other journal in a manner by which their identity could be made out without their permission. Should the identity be not disclosed his consent is not needed.

15. If you are running a nursing home and if you employ assistants to help you the ultimate responsibility rests on you.

16. No physician must exhibit publicly the scale of fees. But there is not objection to the same being put in the physicians' consulting or waiting room.

17. No physician shall use touts or agents for procuring patients.

18. Do not claim to be a specialist unless you have put in a good few years of study and experience or a special qualification in that branch. Once you say you are one, do not undertake work outside your speciality even for your friends.

Appendix II (a)

THE NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential.

   The means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur, except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably (sic) cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Annex I **Appendix II (b)**

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
and the
41st World Medical Assembly Hong Kong, September 1989.

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, " The health of my patient will be my first consideration, "and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical research)

1. In the treatment of the risk person,. the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits. hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods

3. In any medical study, every patient including those of control group, if any -- should be assured of the best proven diagnostic and therapeutic methcd.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1.2)

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers -- either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.